Dossier for *Advair*

This response may include reference to information about Advair Diskus® (fluticasone propionate and salmeterol inhalation powder); Advair® HFA (fluticasone propionate and salmeterol) Inhalation Aerosol.

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This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

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The following indicates sections within the *Advair* dossier where new clinical data has been added to the Dossier within the last year.

Section 2.0 Executive Summary. Includes data supporting expanded indication for COPD (November 2008).

Section 4.2 Dosage Forms and Package Sizes, NDC, WAC Cost per Unit. Updated with new *Advair Diskus* institutional size packages, new dose counter with *Advair* HFA, and current prices. (November 2008)

Section 4.4 FDA Approved Indications. Includes new expanded indication for COPD – reducing exacerbations in patients with COPD. (May 2008)

Section 4.13 Dosing and Administration. Includes updates to the prescribing information for asthma – starting dosage is based on asthma severity. (May 2008)

Section 5.3 Pivotal Efficacy and Safety Trials with *Advair Diskus* in Patients with COPD. Includes results of two pivotal exacerbation studies which support the expanded indication for *Advair Diskus* 250/50 in reducing exacerbations of COPD (May 2008)

Section 6.1 Studies Assessing Serious Asthma-Related Outcomes with Salmeterol-Containing Products in Asthma. Includes the results of two new publications detailing: 1) a meta-analysis of data pooled from 66 GlaxoSmithKline studies evaluating the risk of asthma-related hospitalizations, exacerbations, and deaths with inhaled corticosteroids plus salmeterol compared with inhaled corticosteroids alone and 2) a study in African American patients examining the rate of asthma exacerbations with *Advair* compared with fluticasone propionate alone (September 2008). Includes data that was presented at the FDA Ad-Com Meeting held in December 2008, including results of a meta-analysis of data pooled from over 200 studies, as well as a pediatric sub-analysis (February 2009).

Section 6.2 Studies Assessing Cardiovascular Safety of *Advair*. Includes results from a 12-week safety study of *Advair HFA* in children with asthma. (February 2009)

Section 6.3 Risk of Pneumonia with *Advair* in COPD. Includes the results of two pivotal exacerbations studies with *Advair Diskus* 250/50 and a recently completed meta-analysis with *Advair* (May 2008)

Section 6.4 Studies Assessing Effect on Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression with Advair. Includes results from a 12-week safety study of *Advair HFA* in children with asthma. (February 2009)

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Section 7.2 Comparison with Budesonide Formoterol Combination in Asthma. Includes data from 2 additional studies (i.e., COMPASS and SAM40048) (February 2009).

Section 7.5 Comparison with Montelukast in Children with Asthma. New section to the Dossier (November 2008)

Section 8.4 Use of *Advair HFA* in Children for the Treatment of Asthma. Includes results from a 12-week safety study (February 2009).

Section 9.4 Evidence Table: *Advair* Compared with Budesonide Formoterol Combination in Asthma. Includes data from 2 additional studies (i.e., COMPASS and SAM40048) (February 2009).

Section 9.5 Evidence Table: *Advair Diskus* 250/50 Compared with the Individual Components in COPD. Updated table to include the results of the two pivotal exacerbation studies which support the expanded indication for *Advair Diskus* 250/50 in reducing exacerbations of COPD (May 2008)

Section 10.1 Pharmacoeconomic Evaluation of *Advair* in the Treatment of Asthma. Updated with final study data. (November 2008)

Section 10.3 Effect of *Advair Diskus* on Emergency Room Visits and Hospitalizations in COPD. New section to the Dossier, including information from a state Medicaid database (May 2008)

Section 10.4 Pharmacoeconomic Evaluation of *Advair Diskus* in COPD. Includes 3 pharmacoecomonic studies, including information from a state Medicaid database. (May 2008)

Section 10.5 Compliance/Adherence with *Advair Diskus* in COPD. New section to the Dossier (November 2008)

Section 10.6 Studies Assessing Appropriate Use of *Advair Diskus*. New section to the Dossier (November 2008)

2. EXECUTIVE SUMMARY

DISEASE STATE OVERVIEWS

Asthma

- Asthma is one of the most common chronic diseases in the United States, affecting approximately 22.9 million Americans (6.8 million children) in 2006. The economic cost of asthma in 2005 was estimated at $19.7 billion.(1)
- Asthma is a chronic disease of bronchoconstriction, inflammation and remodeling of the airways. In asthma, airway narrowing and subsequent airflow limitation lead to the symptoms of asthma. Patients with asthma have recurrent episodes of cough (particularly worse at night), wheezing, difficulty breathing, and chest tightness.(2)
- The National Asthma Education and Prevention Program asthma management guidelines recommends to first assess severity in newly diagnosed patients to determine initial therapy. For patients who have been receiving controller medications, the guidelines recommend regular assessments of asthma control for monitoring and adjusting therapy.(2)
- The National Asthma Education and Prevention Program asthma management guidelines recommend the addition of a long-acting beta-agonist to an inhaled corticosteroid as a preferred therapy for patients ≥5 years of age whose asthma is uncontrolled on their current controller and for patients ≥12 years of age with moderate or severe persistent asthma who are new to controller therapy.(2)

Chronic Obstructive Pulmonary Disease (COPD)

- COPD is a common chronic diseases in the United States, affecting approximately 24 million Americans, of which 12 million are physician-diagnosed and 12 million are undiagnosed. The economic cost of COPD in 2007 was estimated at $42.6 billion. COPD is the fourth leading cause of death in the U.S.(3)
- COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. (4,5)
- According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, patients who have dyspnea, chronic cough or sputum production and/or a history of exposure to risk factors should be tested for airflow limitation.(6)
- The GOLD Guidelines recommend 1) inhaled long-acting bronchodilator therapy in patients with FEV_1 <80% predicted, and 2) the addition of an ICS to long-acting bronchodilator therapy in COPD patients with a post-bronchodilator FEV_1 of <50% predicted and a history of repeated exacerbations. These guidelines state that an inhaled corticosteroid combined with a long-acting $beta_2$-agonist is more effective than the individual components in reducing exacerbations and improving lung function.(5,6)

ADVAIR DISKUS: CLINICAL STUDIES IN ASTHMA

Advair Diskus: Efficacy Superior to Fluticasone Propionate or Salmeterol Alone in Asthma

- In two 12-week pivotal trials conducted in the United States in patients 12 years of age and older with asthma, *Advair Diskus* 100/50 and *Advair Diskus* 250/50 provided significantly greater improvements in lung function, symptom scores, and rescue albuterol use compared with fluticasone propionate (FP) inhalation powder or salmeterol inhalation powder alone at the same doses. (7) (8)
  - *Advair Diskus* 100/50 started working as early as Day 1. Reduction in asthma symptoms, rescue albuterol use, and improvement in AM and PM peak expiratory flow (PEF) occurred within Day 1 for both *Advair Diskus* 100/50 and 250/50.
  - *Advair Diskus* 100/50 and 250/50 resulted in significantly fewer patients (3% and 4%, respectively) withdrawing due to worsening asthma in clinical trials compared with patients receiving FP alone (11% and 22%, respectively).

- In a pivotal trial conducted in Europe, patients 12 years of age and older treated with *Advair Diskus* 500/50 had significantly greater improvements in morning peak expiratory flow (PEF) over 12 weeks compared with patients receiving FP inhalation powder 500 mcg alone. (9)

Advair Diskus: Provides Better Asthma Control than Fluticasone Propionate Alone

- The Gaining Optimal Asthma controL (GOAL) study was a 1-year, prospective trial in 3416 patients with uncontrolled asthma that compared the safety and efficacy of step-wise increases of *Advair Diskus* and FP alone in achieving two pre-defined, rigorous composite measures, totally controlled and well-controlled asthma. Both definitions of control were derived from the treatment guidelines of the Global Initiative for Asthma (GINA) and National Institutes of Health (NIH) and were composite measures of several asthma outcomes including PEF, rescue medication use, symptoms, nighttime awakenings, exacerbations, emergency visits, and adverse events. (10)
  - Significantly more patients receiving *Advair Diskus* achieved well-controlled and totally controlled asthma compared with FP regardless of baseline therapy.
  - Patients receiving *Advair Diskus* had significantly fewer exacerbations requiring oral corticosteroids and/or hospitalization or emergency visits than patients receiving FP alone.

Advair Diskus: Use as Initial Maintenance Therapy in the Treatment of Asthma

- *Advair Diskus* 100/50 versus the Individual Components
  - A 12-week, study in 267 patients 12 years of age and older with asthma (FEV_1 40%-85% of predicted) who were symptomatic on short-acting $beta_2$-agonists alone compared *Advair Diskus* 100/50, fluticasone propionate (FP) 100 mcg, or salmeterol 50 mcg twice daily. A significantly greater mean serial FEV_1 AUC at week 12 was observed in patients receiving *Advair* compared with those receiving FP or salmeterol ($P \leq 0.02$), and significantly greater improvement was seen with *Advair* in mean AM predose FEV_1 at study endpoint compared with those receiving salmeterol (primary endpoints). Treatment with *Advair* also resulted in significantly greater improvements in morning PEF, evening PEF, daily asthma symptom scores, and rescue albuterol use compared with both FP and salmeterol alone.(11)
- *Advair Diskus* 100/50 versus Fluticasone Propionate 100mcg
  - A 24-week study in 150 patients 18 years of age and older with asthma treated only with a short-acting $beta_2$agonists compared *Advair Diskus* 100/50 with FP 100 mcg twice daily. Patients were included if they used a short acting bronchodialator at least once per week for asthma symptoms. Patients treated with *Advair* had a significantly higher percentage of symptom-free days and nights (primary endpoint) compared to FP. Improvements in morning and evening PEF, percent of days with no albuterol use, daytime symptom score, percent episode-free days and nights were also significantly higher in patients receiving *Advair*. (12)

Advair Diskus: Efficacy and Safety in Children 4-11 Years Old in Asthma

- In a 12-week clinical study in 303 children 4-11 years of age who were not controlled on FP 100 mcg twice daily, treatment with *Advair Diskus* 100/50 twice daily and FP 200 mcg twice daily resulted in improvement in morning PEF. Non-inferiority of *Advair Diskus* to FP was demonstrated. Additionally, the improvement in mean morning PEF over weeks 1-12 was significantly higher among patients receiving *Advair* compared with higher doses of FP.(13,14)
- *Advair Diskus* 100/50 compared with the use of salmeterol 50 mcg and FP 100 mcg administered separately via Diskus devices provided equivalent improvements in morning peak expiratory flow (PEF) and similar safety profiles over 12 weeks in 257 children 4 to 11 years old.(15)
- *Advair Diskus* 100/50 demonstrated a similar safety profile compared with FP 100 mcg in a 12-week safety study in 203 children 4-11 years old. (16)
- The efficacy of *Advair Diskus* 100/50 in children 4 to 11 years old is also supported by the extrapolation of data from older patients. (7)

ADVAIR DISKUS: HEAD TO HEAD STUDIES IN ASTHMA

Advair Diskus vs. Fluticasone Propionate Plus Salmeterol in Asthma

- Clinical trials in adults and children evaluating *Advair Diskus* versus concurrent FP and salmeterol given in separate inhalers have shown the treatments are comparable across all strengths in regards to efficacy and safety. Although many study endpoints favored *Advair Diskus*, there was no significant difference between treatments. [17,18] [15,19,20]
- A meta-analysis of four pivotal clinical studies that compared *Advair Diskus* with concurrent FP plus salmeterol administered separately found that *Advair Diskus* may result in increased clinical efficacy compared with concurrent therapy. Treatment with *Advair Diskus* resulted in significantly greater improvements in morning peak expiratory flow (PEF) ($P = 0.006$) and evening PEF ($P < 0.001$) compared with concurrent therapy over 12-weeks. [21]

Advair Diskus vs. Budesonide Formoterol Combination in Asthma

- In a 7-month randomized, open-label study, there were no significant differences in exacerbation rates, lung function, asthma symptoms, or rescue medication use in patient receiving stable doses of *Advair Diskus* compared with patients receiving stable doses or adjustable maintenance doses of budesonide formoterol combination (BFC) via metered dose inhaler.[22]
- The efficacy of *Advair Diskus* 250/50 one inhalation twice daily was compared with budesonide formoterol combination (BFC) via Turbuhaler 200/6 mcg, two inhalations twice daily in adult patients with persistent asthma currently receiving inhaled corticosteroids. The primary endpoint, mean rate of exacerbations over the study period, was similar in both treatment groups. Similar improvements in lung function, asthma symptoms, and rescue medication usage were seen with both treatments.[23]
- In a randomized, double-blind, parallel group study (N=248), there was no significant difference in the change in FEV_1 (% predicted) at 12 weeks between treatment with *Advair Diskus* 250/50 compared with budesonide formoterol combination 200/6 mcg via Turbohaler administered twice daily to patients with moderate asthma.[24]

Advair Diskus vs. Higher Doses of Inhaled Corticosteroids in Asthma

- Clinical trials have compared *Advair* with higher doses of inhaled corticosteroids (ICS). [25] [26] These studies have shown *Advair* to provide superior efficacy results compared with higher doses of ICS.
  - In a comparison study of patients symptomatic on moderate doses of inhaled corticosteroids (N=365), patients who received *Advair Diskus* 250/50 twice daily had significant improvements in peak expiratory flow (PEF), symptom-free days, and a reduction in albuterol use compared with patients receiving double the dose of FP, 500 mcg twice daily.[25]
  - In a 12-week clinical study in 154 patients who were uncontrolled on a short-acting $beta_2$-agonist alone, initiating controller therapy with *Advair Diskus* 100/50 twice daily showed significant improvements in mean morning PEF compared to patients initiating therapy with FP 250 mcg twice daily. [26]

Advair Diskus vs. Montelukast in Asthma

- Two 12-week clinical trials in patients with asthma who were symptomatic on short-acting beta-agonists alone (mean baseline 4-5 puffs of albuterol per day) have shown that initial therapy with *Advair Diskus* 100/50 twice daily provided improved overall asthma control as measured by albuterol use, symptoms and lung function compared with treatment with montelukast 10 mg once a day regardless of baseline asthma severity. [27,28] [29]
- In a 12-week, randomized, double-blind, parallel-group study, the safety and efficacy of *Advair Diskus* 100/50 twice daily was compared to montelukast 5 mg once daily in 548 children 6 to 14 years of age. The children included were previously symptomatic on short-acting $beta_2$ agonists alone and had an FEV_1 55-80% of predicted. Children receiving *Advair* had significant improvements in lung function, asthma symptoms, albuterol use, and well-controlled asthma weeks compared with those receiving montelukast. Similar improvements in nights with no awakenings were seen in both treatment groups.

Advair Diskus vs. Montelukast in Children with Asthma

- In a 12-week, randomized, double-blind, parallel-group study, the safety and efficacy of *Advair Diskus* 100/50 twice daily was compared to montelukast 5 mg once daily in 548 children 6 to 14 years of age. The children included were previously symptomatic on short-acting beta$_2$-agonists alone and had an FEV_1 55-80% of predicted. Children receiving *Advair* had significant improvements in lung function, asthma symptoms, albuterol use, and well-controlled asthma weeks compared with those receiving montelukast. Similar improvements in nights with no awakenings were seen in both treatment groups. Both treatments were generally well tolerated with a similar incidence of adverse events reported in each group. Asthma exacerbations were lower in the *Advair* treatment group compared with montelukast.(30)

Advair Diskus vs. Montelukast Plus Fluticasone Propionate in Asthma

- In two, similar, 12-week, randomized, double-blind, double-dummy, parallel-group studies in patients who were symptomatic on low dose FP, *Advair Diskus* 100/50 twice daily resulted in significantly greater improvements in lung function compared with the addition of montelukast 10 mg once daily to FP inhalation powder 100 mcg twice daily. (31) (32)

***ADVAIR DISKUS*: STUDIES ASSESSING COMPLIANCE IN ASTHMA**

- In two similarly designed, retrospective studies using medical and pharmacy claims data from managed care organizations in the U.S., the prescription refill rate for *Advair Diskus* was significantly higher than the refill rates of FP [patients were treated with FP plus salmeterol, FP plus montelukast, or FP alone]. These results suggest that the use of *Advair Diskus* may increase ICS refill persistence. There was not a difference in the refill rate for *Advair Diskus* versus montelukast (used as a single controller medication). (33) (34)
- A retrospective, observational study was conducted using medical and pharmacy claims data from a large health insurance claims database to determine refill persistence in patients stepped-up from an ICS to combination therapy with *Advair Diskus*, ICS + salmeterol, or ICS + montelukast. Compared with patients who added on salmeterol or montelukast, patients switched to *Advair Diskus* had a significantly greater mean ICS refill rate and mean medication possession ratio in the 12 months post-switch.(35)
- Based on results from a retrospective study evaluating refill persistence in pediatric patients (4-17 years old) in a managed care organization in the U.S., patients receiving *Advair Diskus* had significantly higher mean refill rates over 12 months compared with FP alone, ICS plus salmeterol, and ICS plus montelukast.(36)
- Results of a retrospective, longitudinal analysis including approximately 13,000 patients showed that increased adherence to *Advair Diskus* was associated with a reduced risk of asthma-related emergency department visits or hospitalizations.(37)

***ADVAIR DISKUS*: ECONOMIC STUDIES IN ASTHMA**

- Two retrospective observational studies have evaluated the risk of hospitalizations/emergency department (ED) visits in patients receiving *Advair Diskus* compared with FP. One study in 2,414 patients showed patients receiving *Advair Diskus* had a reduction in the combined endpoint of asthma-related hospitalizations and ED visits compared with FP alone. A second study in 64,689 patients showed patients receiving FP had a higher rate of asthma-related ED visits compared with patients receiving *Advair Diskus*. (38,39)
- Results of a 1-year, retrospective, observational study showed that in patients receiving an inhaled corticosteroid (ICS), switching to *Advair Diskus* was associated with significantly reduced treatment failure (asthma-related ED visit/hospitalization, or receipt of oral corticosteroid [OCS] or other class of asthma controller) and significantly lower total costs of asthma-related care compared with ICS plus salmeterol or ICS plus montelukast.(40) Total asthma-related costs were 13% and 21% lower with *Advair*-treated patients compared with ICS plus salmeterol and ICS plus montelukast, respectively.
- Several cost-effectiveness analyses demonstrated that *Advair Diskus* 100/50 twice daily is more cost-effective than montelukast 10 mg once daily plus FP 100 mcg twice daily in symptomatic

patients with persistent asthma receiving ICS therapy, and montelukast alone as initial maintenance therapy for persistent asthma. (41) (42) (43,44)

ADVAIR DISKUS: CLINICAL STUDIES IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Advair Diskus 250/50: Better Improvements in Lung Function in COPD

- In a 6-month, randomized, double-blind, placebo-controlled, parallel-group study of 723 patients, the efficacy and safety of twice-daily *Advair Diskus* 250/50 in the treatment of COPD was evaluated in a comparison with FP 250 mcg, salmeterol 50 mcg, and placebo. (45)
  - Patients treated with *Advair* experienced a significantly greater improvement in predose FEV_1 from Baseline to Endpoint (165 mL) compared with those treated with salmeterol 50 mcg (91 mL, P=0.012). A significant improvement in two-hour postdose FEV_1 was observed in patients treated with *Advair* (281 mL) compared to those treated with FP 250 mcg (147 mL, P<0.001) (primary endpoints).
  - At day 1, significantly greater increases in two-hour postdose FEV_1 values were observed for treatment with *Advair* (206 mL) compared with that for FP (70 mL; P <0.001) and placebo (54 mL; P<0.001). A greater increase in predose FEV_1 was seen at Week 1 with *Advair* (165 mL) compared with salmeterol 50 mcg (122 mL, P=0.026).

Advair Diskus 250/50: Reduces COPD Exacerbations

- Two replicate, 12-month, randomized, double-blind, parallel-group studies compared the effect of *Advair Diskus* 250/50 with salmeterol 50 mcg each administered twice daily on the annual rate of moderate/severe exacerbations (primary endpoint) in 1579 patients with COPD with a history of COPD exacerbations. COPD exacerbations that required treatment with oral corticosteroids, antibiotics, or hospitalization were defined as moderate/severe.(46,47)
  - The annual rate of moderate/severe COPD exacerbations was significantly lower by approximately 30% in the group treated with *Advair* compared with salmeterol.
  - In each study the number of patients needed-to-treat (NNT) to prevent one moderate/severe exacerbation per year was 2.
  - In both studies, patients receiving *Advair* had a significant reduction in risk of time to first moderate/severe exacerbation and a reduction in the rate of exacerbations requiring oral corticosteroids compared with salmeterol.

Advair Diskus 500/50: Effects on Mortality, Exacerbations, Quality of Life, and Lung Function in COPD

- The TORCH study was a three-year, randomized, double-blind, placebo-controlled study of over 6000 patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). Patients were randomized to three years of twice-daily treatment with either *Advair Diskus* 500/50, FP 500 mcg, salmeterol 50 mcg, or placebo.(48)
  - Use of *Advair Diskus* 500/50 resulted in a 17.5% reduction in the risk of dying anytime over three years compared with placebo (P=0.052).
  - Use of *Advair Diskus* resulted in a reduced rate of moderate/severe COPD exacerbations by 25% compared with placebo (P<0.001), by 12% vs. salmeterol (P=0.002), and by 9% vs. FP (P=0.02).
  - Use of *Advair Diskus* 500/50 resulted in a statistically significant (P<0.001) but not clinically significant (-3.1 units [change of 4 units considered clinically significant]) improvement in quality of life score as measured by the St. George's Respiratory Questionnaire (SGRQ) compared with placebo.
  - Over the entire three-year treatment period, improvements in lung function were larger in the *Advair Diskus* group than the placebo group and both of the other active treatment groups (P<0.001).
  - A *post hoc* analysis was performed to investigate the effects of treatment on rate of decline in FEV_1. Rate of decline was significantly reduced by *Advair Diskus* compared with placebo ($P \leq 0.003$).(49)

ADVAIR DISKUS: HEAD TO HEAD STUDIES IN COPD

Advair Diskus vs. Tiotropium in COPD

- A 2-year, randomized, double-blind, double-dummy study compared *Advair Diskus* 500/50 twice daily with tiotropium 18 mcg once daily in 1,323 patients with severe COPD.[50]
  - No statistically significant difference between treatment groups was observed in the primary endpoint of COPD-related exacerbations requiring oral corticosteroids, antibiotics or hospitalization.
  - Patients receiving *Advair* were significantly less likely to withdraw from the study at any time compared with tiotropium.
  - Additionally, patients receiving *Advair* had a significant reduction in the rate of patients experiencing exacerbations requiring oral corticosteroids; however, patients receiving tiotropium were less likely to have an exacerbation requiring antibiotics.
  - Mortality was assessed as an other efficacy endpoint. *Advair Diskus* reduced the risk of dying on therapy at any time within 2 years by 52% compared with tiotropium (P=0.012).
  - No other differences were noted in any of the other secondary efficacy endpoints.

Advair Diskus vs. Ipratropium Plus Albuterol in COPD

- The efficacy and safety of *Advair Diskus* 250/50 twice daily in the treatment of patients with COPD was compared with that of ipratropium/albuterol via metered-dose inhaler 2 puffs (36 mcg/206 mcg) four times a day in two identically designed multicenter, randomized, double-blind, double-dummy, parallel-group, 8-week studies. [51] [52]
  - In both studies, *Advair Diskus* 250/50 was superior to ipratropium/albuterol in the primary efficacy outcome of change from baseline at Endpoint in morning pre-dose forced expiratory volume in one second (FEV_1).
  - In both studies, the changes from baseline at Endpoint in the secondary outcomes of morning peak expiratory flow, 6-hour FEV_1 area-under-the-curve (FEV_1 AUC_6), and dyspnea as measured by the Transition Dyspnea Index (TDI) score were significantly greater with *Advair Diskus* 250/50.

ADVAIR : CONCURRENT THERAPY IN COPD

Advair Plus Tiotropium in COPD

- In a 1-year randomized, parallel-group study including 449 patients with COPD (FEV_1 <65% of predicted), no statistically significant difference was seen between combination therapy with *Advair HFA* plus tiotropium bromide or salmeterol plus tiotropium compared with placebo plus tiotropium in the proportion of patients with one or more COPD exacerbations, mean exacerbations per patient-year, or the number of COPD exacerbations resulting in a physician or ED visit. However, patients receiving *Advair HFA* plus tiotropium had significantly fewer COPD exacerbations resulting in hospitalization and hospitalizations from any cause, as well as significant improvements in lung function and quality of life compared with tiotropium plus placebo.[53]
- In a 3-month, randomized, double-blind, double-dummy, parallel-group study of 90 patients with COPD (FEV_1 <50% of predicted), the combination of *Advair Diskus* 500/50 twice daily and tiotropium bromide 18 mcg once daily resulted in significantly greater improvements in pre-dose FEV_1 than either drug alone, but differences in dyspnea score and rescue albuterol use were not significant.[54]

ADVAIR DISKUS: STUDIES ASSESSING COMPLIANCE IN COPD

- Two similarly designed, retrospective, cohort studies of medical and pharmacy claims data from large managed care or healthcare plan databases evaluated refill rates in patients with COPD who were receiving their initial maintenance medication. The refill rate for *Advair Diskus* 250/50 was significantly higher than salmeterol alone, ICS alone, ipratropium plus albuterol, or ipratropium alone. Initial maintenance therapy with *Advair Diskus* 250/50 was associated with a significant lower risk of hospitalization or ED visit compared with ipratropium alone. In one of the studies, therapy with *Advair Diskus* was related to lower medical costs, higher pharmacy costs, and similar total costs.[55,56]

ADVAIR DISKUS: ECONOMIC STUDIES IN COPD

- Costs
  - An analysis of a Texas Medicaid database demonstrated that patients taking *Advair Diskus* had significantly lower all-cause and COPD-related medical (hospitalization and ED visits) costs compared with those taking ipratropium. Alternatively, patients taking *Advair Diskus* had higher total pharmacy costs (both all-cause and COPD-related).[57]
  - In retrospective, observational analyses of large health care benefit plan databases (Integrated Healthcare Information Services and PharMetrics Patient Centric Database), pharmacoeconomic and healthcare resource utilization evaluations were conducted to compare treatments in patients with COPD receiving initial therapy with *Advair Diskus* versus other inhaled maintenance medications.[55,56,58]
    - In separate analyses of these databases, initial maintenance therapy with *Advair Diskus* was associated with significantly lower COPD-related medical costs in patients with COPD compared with ipratropium despite higher pharmacy costs with *Advair Diskus*.
    - Pharmacy costs were significantly higher with *Advair Diskus,* partly due to increased treatment adherence and refill rates.
- Healthcare Resource Utilization
  - An analysis of a Texas Medicaid database also found that initial maintenance therapy with *Advair Diskus* was associated with significantly lower all-cause hospitalizations/emergency department (ED) visits and lower COPD-related hospitalizations/ED visits compared with ipratropium.[57]
  - In retrospective, observational analyses of large health care benefit plan databases (Integrated Healthcare Information Services and PharMetrics Patient Centric Database), pharmacoeconomic and healthcare resource utilization evaluations were conducted to compare treatments in patients with COPD receiving initial therapy with *Advair Diskus* versus other inhaled maintenance medications.[55,56,58]
    - In separate analyses of these databases, initial maintenance therapy with *Advair Diskus* was associated with significantly lower all-cause hospitalizations/emergency department (ED) visits and lower COPD-related hospitalizations/ED visits compared with ipratropium.

STUDIES ASSESSING APPROPRIATE USE OF *ADVAIR DISKUS*

- Retrospective, observational, cohort analyses of administrative claims databases were conducted to assess the proportion of patients with documentation in their claims history that could identify them as appropriate candidates for use of *Advair Diskus*. These analyses were conducted using patient-level data from pharmacy claims that were linked with medical claims and eligibility information. Criteria for appropriate use included prior use of inhaled corticosteroid-containing medication, prior treatment by a specialist (pulmonologist or allergist), prior asthma-related ED visit or hospitalization, and prior COPD diagnosis.[59,60]
  - In an analysis of a multi-plan managed care database, 90% of patients prescribed *Advair Diskus* had evidence in their claims history that could identify them as appropriate candidates for *Advair Diskus*.[59]
  - In an analysis of a multi-state Medicaid database, 94% of patients prescribed *Advair Diskus* had evidence in their claims history that could identify them as appropriate candidates for *Advair Diskus*.[60]

ADVAIR HFA: CLINICAL STUDIES IN ASTHMA

- *Advair HFA* has comparable efficacy and safety with *Advair Diskus*.[61]
- In three 12-week, pivotal efficacy trials in adult and adolescent patients 12 years of age and older with asthma, patients receiving *Advair HFA* 45/21 or *Advair HFA* 115/21 had significant improvements in lung function compared with patients receiving similar doses of FP and/or salmeterol alone.[62,63] [64]
- Two randomized, double-blind, double-dummy, 12-week studies, each enrolling 500 adults and adolescents with asthma, compared the safety and efficacy of *Advair HFA*, *Advair Diskus*, and fluticasone propionate (FP) administered via CFC containing metered dose inhaler (MDI).

Both studies found that the two *Advair* formulations were equivalent in terms of improving morning/evening peak expiratory flow rate (PEFR), increasing the percent of symptom-free days and increasing the percent of days free of rescue medication. *Advair HFA* was found to be significantly better than FP for all of these outcomes.[65,66]

- A 12-week, multicenter, randomized, double-blind, double-dummy, parallel group study compared *Advair Diskus* 100/50 one inhalation twice daily and *Advair* HFA 50/25 (dose expressed as ex-valve) two inhalations twice daily to demonstrate clinical equivalence between the two formulations in children with asthma. The study included 428 pediatric patients 4-11 years of age who were receiving an ICS (beclomethasone, budesonide, or flunisolide ≤500 mcg/day or fluticasone propionate ≤200 mcg/day) for at least 4 weeks before the run-in period. For the primary endpoint, mean AM PEF improvement from baseline was 37.7 L/min and 38.6 L/min in the groups treated with *Advair Diskus* and *Advair* HFA, respectively, which was within the predefined criteria for equivalence.
- A 12-week, randomized, double-blind, double-dummy study compared the safety of treatment with *Advair HFA* 50/25 two inhalations twice daily and fluticasone propionate (FP) HFA inhalation aerosol 50 mcg two inhalations twice daily in 350 patients ages 4 to 11 years. The incidence and type of adverse events were similar between treatment groups. Other safety parameters evaluated including vital signs, electrocardiogram (ECG) changes, urinary cortisol, laboratory findings, and asthma exacerbations showed a comparable safety profile between *Advair HFA* and FP.[67]

***ADVAIR*: IMPORTANT SAFETY INFORMATION**

- **BOXED WARNING:** Long-acting beta$_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in *Advair*, may increase the risk of asthma related death.[68] Therefore, when treating patients with asthma, physicians should only prescribe *Advair* for patients not adequately controlled on other asthma controller medications (e.g., low- to medium dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. Data from a large placebo controlled US study, Salmeterol Multicenter Asthma Research Trial (SMART), that compared the safety of salmeterol (Serevent® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). [69]
- Data from the SMART trial are not adequate to determine if concurrent use of ICS, such as FP, or other controller therapy modifies the risk of asthma-related death.[61,68]
- Results of a meta-analysis of over 200 studies and over 100,000 patients found that salmeterol when used in the absence of an inhaled corticosteroid (ICS) or with background ICS that was not part of study treatment may be associated with an increased risk of serious asthma events including asthma-related hospitalization, intubation and death. However, when salmeterol was used in combination with an ICS as study treatment or as *Advair*, no increased risk was evident. There were no asthma-related deaths or intubations in patients receiving *Advair*.[70]
- A meta-analysis of 66 GlaxoSmithKline studies worldwide in more than 20,000 patients has shown no increased risk of asthma-related hospitalization in patients receiving an inhaled corticosteroid (ICS) plus salmeterol compared with an ICS alone. There was one asthma-related intubation in a patient receiving beclomethasone dipropionate plus salmeterol and one asthma-related death in a patient receiving FP plus salmeterol concomitantly. No asthma-related deaths were reported in patients while receiving FP plus salmeterol in a single device.[71]
- In a 1-year, randomized, double-blind trial in 427 African American patients, the rate of asthma exacerbations was lower but not statistically significantly different in patients treated with *Advair* 100/50 (0.449 per year) compared with FP 100 mcg (0.529 per year, P= 0.169). No increased risk of serious adverse effects in African American patients was noted with *Advair Diskus* as compared with FP. Two patients treated with *Advair* and three patients treated with FP were hospitalized due to an asthma exacerbation, and no deaths occurred during the study.[72]
- *Advair* does not replace fast-acting inhalers to treat acute symptoms.[68]
- *Advair* should not be initiated in patients during rapidly deteriorating or potentially life threatening episodes of asthma or COPD. Increasing use of inhaled short-acting beta$_2$-agonists is a marker of deteriorating asthma. The physician and patient should be alert to such changes.

- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD with a history of exacerbations, as the clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and *Advair Diskus*. In COPD trials, the incidence of pneumonia in patients treated with *Advair Diskus* was higher in patients over 65 years of age compared to the incidence in patients under 65 years of age.
- Oral candidiasis has been observed in clinical studies in patients treated with *Advair*. Instruct patients to rinse the mouth after each inhalation.
- Patients using *Advair* should not use additional long-acting $beta_2$-agonists (eg, salmeterol, formoterol) for any reason.
- Patients with COPD often have multiple risk factors for reduced bone mineral density. *Advair Diskus* may increase this risk; therefore, bone mineral density assessment is recommended prior to starting *Advair Diskus* and periodically thereafter.
- Long-term use of inhaled corticosteroids, including *Advair Diskus*, may increase the risk for cataracts or glaucoma. Regular eye exams should be considered.
- Advair should NOT be used for transferring patients from systemic corticosteroid therapy to inhaled corticosteroids, as adrenal insufficiency may occur.
- The use of strong cytochrome P450 3A4 inhibitors (e.g., ritonavir) with *Advair* is not recommended.
- *Advair Diskus* may increase blood pressure and heart rate. It should be used with caution in patients with cardiovascular disorders (especially coronary insufficiency, cardiac arrhythmias, and hypertension), thyrotoxicosis, or convulsive disorders.
- *Advair* contains an inhaled corticosteroid. Inhaled corticosteroids, as well as poorly controlled asthma, may cause a reduction in growth velocity. The long-term effect on final adult height is unknown.
- The most common adverse events (≥5%) reported in asthma clinical trials with *Advair Diskus* 100/50 (and placebo) in patients ≥12 years of age were: upper respiratory infections 27% (14%), pharyngitis 13% (6%), headache 12% (7%), upper respiratory inflammation 7% (5%), and dysphonia 5% (<1%).
- *Advair Diskus* 100/50 and FP 100 mcg had similar adverse events in a 12-week safety study in 203 children 4 - 11 year of age. Common adverse reactions (≥3% and greater than placebo) seen in the pediatric patients but not reported in the adult and adolescent clinical trials included: throat irritation and ear, nose, and throat infections.
- In patients with COPD, the most common adverse events (≥5%) reported in a 6-month clinical trial with *Advair Diskus* 250/50 (and placebo) were headache, 16% (12%); candidiasis mouth/throat, 10% (1%); musculoskeletal pain, 9% (9%); throat irritation, 8% (7%); lower viral respiratory infections, 6% (3%); and hoarseness/dysphonia, 5% (0%).
- The most common adverse events reported in clinical trials with *Advair HFA* 45/21, 115/21 compared with placebo were: upper respiratory tract infection 16%, 24%, 13%; headache 21%, 15%, 11%; throat irritation 9%, 7%, 7%; and musculoskeletal pain 5%, 7%, 4%, respectively.

ADVAIR PRODUCT DESCRIPTION

- *Advair Diskus* and *Advair HFA* Inhalation Aerosol contain a combination of a corticosteroid (fluticasone propionate) and a long-acting $beta_2$-adrenergic agonist bronchodilator (salmeterol) for inhalation.

Indications

- *Advair Diskus*
  - Maintenance Treatment of Asthma
    - *Advair Diskus* is indicated for the long-term, twice-daily, maintenance treatment of asthma in patients 4 years of age and older. Long-acting $beta_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in *Advair Diskus*, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe *Advair Diskus* for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or

whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies.
    - Important Limitations of Use:
        - *Advair Diskus* is NOT indicated for the relief of acute bronchospasm
        - *Advair Diskus* is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short acting $beta_2$ agonists.
  - Maintenance Treatment of Chronic Obstructive Pulmonary Disease
    - *Advair Diskus* 250/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. *Advair Diskus* 250/50 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. *Advair Diskus* 250/50 twice daily is the only approved dosage for the treatment of COPD because an efficacy advantage of the higher strength *Advair Diskus* 500/50 over *Advair Diskus* 250/50 has not been demonstrated.
    - Important Limitations of Use:
        - *Advair Diskus* is NOT indicated for the relief of acute bronchospasm.
- *Advair* HFA
  - *Advair* HFA is indicated for the long-term, twice-daily maintenance treatment of asthma in patients 12 years of age and older. Long-acting $beta_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in *Advair* HFA, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe *Advair* HFA for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. *Advair* HFA is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting $beta_2$-agonists. *Advair* HFA is NOT indicated for the relief of acute bronchospasm.

Dosage

- *Advair Diskus*
  - For the maintenance treatment of asthma in patients ≥12 years, *Advair Diskus* is dosed 1 inhalation of 100/50, 250/50, or 500/50 twice daily; starting dosage is based on asthma severity.
  - For the maintenance treatment of asthma in patients 4 to 11 years, *Advair Diskus* is dosed 1 inhalation of 100/50 twice daily.
  - For the maintenance treatment of COPD, *Advair Diskus* is dosed 1 inhalation of 250/50 twice daily.
- *Advair* HFA
  - For the maintenance treatment of asthma in patients ≥12 years, *Advair* HFA is dosed 2 inhalations of 45/21, 115/21, 230/21 twice daily; starting dosage is based on asthma severity.

Pharmacology

- Fluticasone propionate
  - Fluticasone propionate is a trifluorinated corticosteroid with potent anti-inflammatory activity. *In vitro* assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.
  - The precise mechanism of action of inhaled corticosteroids, like fluticasone propionate, in asthma is unknown. Corticosteroids have been associated with improvements in most of the pathophysiologic changes associated with asthma such as inhibition of multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) involved in the asthmatic response and the mediators they produce (e.g., histamine, eicosanoids, leukotrienes,

and cytokines).[73] In addition, evidence has suggested that ICS may have effects on reversing some aspects of airway remodeling. [74] [75] [76]

- Inflammation is also a component in the pathogenesis of COPD. In contrast to asthma, however, the predominant inflammatory cells in COPD include neutrophils, CD8+ T lymphocytes, and macrophages. The effects of corticosteroids in the treatment of COPD are not well defined.

- Salmeterol
  - Salmeterol is a selective, long-acting beta$_2$-adrenergic agonist. The pharmacologic effects of β_2-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic 3', 5' adenosine monophosphate (cyclic AMP).[77] Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from mast cells and other inflammatory cells. Data suggests that salmeterol also exerts other non-bronchodilator effects that may contribute to its therapeutic effects in the treatment of asthma. [78]

SUMMARY OF BENEFITS OF *ADVAIR DISKUS*

- *Advair Diskus* is the only inhaled corticosteroid/bronchodilator combination product approved for both asthma and chronic obstructive pulmonary disease (COPD).
- *Advair Diskus* 250/50 is the first and only treatment approved by the FDA to reduce exacerbations in patients with COPD.
- *Advair Diskus* is the only inhaled corticosteroid/bronchodilator combination product approved for pediatric patients with asthma (age 4-11 years).
- *Advair* is the only inhaled corticosteroid/bronchodilator combination product available in both a dry powder formulation and a pressurized metered dose inhaler (MDI) formulation.
- *Advair* is the only inhaled corticosteroid/bronchodilator combination product available in three strengths (both dry powder and MDI formulations).
- Both the dry powder formulation and the pressurized metered dose inhaler formulation are available with a built-in dose counter.
- With the *Diskus* device, even patients with severe lung dysfunction (FEV_1 20% to 30% of predicted) can achieve an inspiratory airflow rate sufficient to receive an effective dose.
- There have been more than 88 million prescriptions dispensed for *Advair Diskus* since its introduction in 2001.

3. DISEASE DESCRIPTION

Asthma: Epidemiology and Risk Factors

Asthma is one of the most common chronic diseases in the United States. According to the American Lung Association's Trends in Asthma Morbidity and Mortality report, approximately 22.9 million Americans (6.8 million children) had asthma in 2006.[1] In addition, 12.4 million people, or 54% of the people who had asthma at the time of the survey, had experienced an asthma attack in the previous year. Health care use in 2005 included 488,594 asthma-related hospitalizations and approximately 1.8 million emergency department visits. Deaths from asthma in 2005 numbered 3,884.[79] The economic cost of asthma in 2005 was estimated at $19.7 billion.[1]

Atopy, the genetic susceptibility for the development of an IgE-mediated response to environmental allergens, is the strongest identifiable predisposing factor for developing asthma.[2]

Asthma: Pathophysiology

Asthma is a chronic disease of bronchoconstriction, inflammation and remodeling of the airways.[2] In asthma, airway narrowing and subsequent airflow limitation lead to the symptoms of asthma. In an acute exacerbation, contraction of the bronchial smooth muscle, or bronchoconstriction, occurs in response to exposure to an inhaled allergen or irritant. The inflammatory reaction to an inhaled allergen involves a complex interaction of a variety of cells, including mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, smooth muscle cells, and epithelial cells. As inflammation becomes more progressive and the disease becomes more persistent, factors such as edema, inflammation, mucus hypersecretion, and

hypertrophy and hyperplasia of the airway smooth muscle lead to further airflow obstruction. In addition, airway inflammation results in an increase in the existing airway hyperresponsiveness. Over time, permanent structural changes may occur which result in loss of lung function that may be only partially reversible with therapy, also known as airway remodeling. Some of the structural changes which may occur include thickening of the sub-basement membrane, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and secretion. The interaction between symptoms, airway obstruction, bronchial hyperresponsiveness, and inflammation determines the clinical manifestations and severity of asthma as well as the response to treatment.

Asthma: Clinical Presentation

Patients with asthma have recurrent episodes of cough (particularly worse at night), wheezing, difficulty breathing, and chest tightness.(2) These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. Patients also experience bronchial hyperresponsiveness to various triggers. On physical examination, patients may exhibit hyperexpansion of the thorax (especially in children), use of accessory muscles, hunched shoulders, and chest deformity. Wheezing may occur during normal breathing or during a prolonged phase of forced exhalation, although wheezing may be absent between exacerbations. Patients may have increased nasal secretion, mucosal swelling and nasal polyps. In addition, atopic dermatitis/eczema or any other allergic skin condition may be present. Symptoms may be absent during the time of examination; therefore, a history of symptoms is important.

Asthma: National Asthma Education and Prevention Program Guidelines

The 2007 National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma recommend to first assess severity in newly diagnosed patients to determine initial therapy for patients with asthma.(2) For patients who have been receiving long-term controller medications, the guidelines recommend regular assessments of asthma control for monitoring and adjusting therapy. The guidelines provide impairment and risk criteria to assess both asthma severity and asthma control for each of the three age ranges: 0-4 years of age, 5-11 years of age, and ≥12 years of age. Impairment is defined as the frequency and intensity of symptoms and functional limitations the patient is experiencing or has recently experienced. Risk is defined as the likelihood of either asthma exacerbations, progressive decline in lung function, or risk of adverse effects from a medication. In addition, the guidelines also recognize the use of validated assessment tools, like the Asthma Control Test and Childhood Asthma Control Test, to assess asthma control.

For each age range, there are six treatment steps which provide preferred, and for some steps alternative, treatment recommendations for both intermittent and persistent types of asthma. All patients, regardless if they have intermittent or persistent asthma, should receive a short-acting $beta_2$-agonist for quick relief of their asthma symptoms. Inhaled corticosteroids, either alone or in combination with other controller medications, continue to be the preferred first-line therapy for children and adults with persistent asthma. The guidelines also recommend the use of a long-acting beta-agonist (LABA) and an inhaled corticosteroid (ICS) as a preferred therapy for patients ≥5 years of age whose asthma is uncontrolled on their current controller and for patients ≥12 years of age with moderate to severe persistent asthma who are new to controller therapy.

COPD: Epidemiology and Relevant Risk Factors

Risk factors for COPD include cigarette smoking, environmental pollutants, and genetic factors such as α-$_1$ antitrypsin deficiency. Cigarette smoking accounts for approximately 90% of all COPD cases. (4) Smokers who are diagnosed with COPD have a rate of decline in forced expiratory volume in one second (FEV_1) that is 2 to 3 times that of non-smokers. (80)

According to the World Health Organization, by 2020 COPD will rise from the 12th to the 5th most prevalent disease and from the 6th to the 3rd most common cause of death worldwide. (81) The COPD in America Survey found that patients underestimated their symptom severity and overestimated their degree of disease control, which may lead to suboptimal disease management and a lower quality of life than necessary.(82)

COPD is a leading cause of morbidity and mortality and results in an economic and social burden that is both substantial and increasing.[5] COPD is often associated with acute exacerbations of symptoms that range from increased dyspnea and increased productive cough to acute respiratory failure. Reports suggest that patients experience exacerbations regularly (e.g., median rates of 2.4 and 3 episodes per year).[83,84] Hospital mortality of patients admitted for an acute exacerbation of COPD is approximately 10%.[85,86] Also, the long-term outcome is poor with mortality reaching 40% in one year.[85,87] A study evaluating 1,016 patients who were hospitalized for acute exacerbations showed that those who survived the first hospitalization had a 50% rate of rehospitalization within 6 months after discharge.[85] The direct and indirect costs of COPD to the U.S. in 2007 were estimated to be about $42.6 billion.[3]

COPD: Pathophysiology

COPD is a disease state characterized by airflow limitation that is not fully reversible. [4,5] The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The term COPD was introduced because chronic bronchitis and emphysema often coexist. It may, therefore, be difficult in an individual case to determine which is the major condition. Chronic bronchitis is defined as the presence of cough and sputum production for at least 3 months in each of two consecutive years. Emphysema, or destruction of the alveoli, is a pathological term that describes one of several structural abnormalities present in patients with COPD.

The chronic inflammation of COPD exists throughout the airways and parenchyma.[5] The intensity and cellular and molecular characteristics of the inflammation vary as the disease progresses. Over time, inflammation damages the lungs and leads to the pathologic changes characteristic of COPD. Key inflammatory cells include neutrophils, macrophages, and CD8+ T-lymphocytes.[6] There may also be an increase in eosinophils in some patients, particularly during exacerbations. Activated inflammatory cells in COPD release a variety of mediators, notably leukotriene B_4 (LTB_4), interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF-α), and are thought to damage lung structures and/or sustain neutrophilic inflammation. In addition to inflammation, an imbalance of proteases and antiproteases in the lung and oxidative stress are two important pathogenic processes. These processes may themselves be consequences of inflammation, or they may arise from environmental or genetic factors. The lung has natural defense mechanisms, but genetic traits (e.g., alpha-1 antitrypsin deficiency), exposure to other environmental risk factors (e.g., infection, atmospheric pollution), the chronic nature of the inflammation, or the repeated nature of the injury may cause the irreversible breakdown of defenses.

COPD: Clinical Presentation

Throughout the course of the disease, physiological changes develop : mucus hypersecretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension, and cor pulmonale.[6] Initially, cough may be intermittent, but often becomes persistent or present every day. Chronic sputum production may also indicate COPD. Breathlessness or dyspnea is often considered the hallmark symptom of COPD and is often persistent (present every day) and progressive (worsens over time). Dyspnea is the symptom that causes most patients to seek medical attention, and is a major cause of disability and anxiety associated with the disease. Wheezing and chest tightness may also be present.

COPD: Approaches to Treatment-Principle Options/Practice Patterns

The increase in awareness and development of treatment recommendations for COPD to decrease morbidity and mortality are important goals of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines, initiated by the U.S. National Heart, Lung, and Blood Institute and the World Health Organization.[6] According to the GOLD guidelines, patients who have dyspnea, chronic cough or sputum production and/or a history of exposure to risk factors should be tested for airflow limitation. For the diagnosis and assessment of COPD, spirometry is the standard of care. An $FEV_1/FVC < 0.70$ and a post-bronchodilator $FEV_1 < 80\%$ of predicted confirms the presence of airflow limitation that is not fully reversible.

The GOLD Guidelines recommend long-acting inhaled bronchodilator therapy in those patients with $FEV_1 < 80\%$ predicted and recognize that long-acting inhaled bronchodilators are more effective and convenient.[6] The GOLD Guidelines also recommend the addition of an inhaled corticosteroid (ICS) to long-acting inhaled bronchodilator therapy in COPD patients with a postbronchodilator FEV_1 of <50%

predicted and a history of repeated exacerbations. Regular treatment with an ICS reduces the frequency of exacerbations and improves health status.

Table 1. Therapy at Each Stage of COPD[5]

Stage	Characteristics	Recommended Treatment
I: Mild COPD	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted	Active reduction of risk factors; influenza vaccination Add: Short-acting bronchodilator when needed
II: Moderate COPD	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted	Add: Regular treatment with one or more long-acting bronchodilators Rehabilitation
III: Severe COPD	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted	Add: Inhaled corticosteroids if repeated exacerbations
IV: Very Severe COPD	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ plus chronic respiratory failure	Add: Long-term oxygen therapy if respiratory failure Consider surgical treatments

4. PRODUCT DESCRIPTION

4.1 Generic Name, Brand Name and Therapeutic Class

GENERIC NAMES:

Advair Diskus (fluticasone propionate and salmeterol inhalation powder)

Advair HFA Inhalation Aerosol (fluticasone propionate and salmeterol)

BRAND NAMES: ADVAIR DISKUS® and ADVAIR® HFA INHALATION AEROSOL

THERAPEUTIC CLASS: Combination of a corticosteroid and a long-acting $beta_2$-adrenergic bronchodilator for inhalation

4.2 Dosage Forms and Package Sizes, NDC, WAC Cost per Unit

Table 2. *Advair Diskus:* Dosage Forms/NDC/Wholesale Acquisition Cost

Dosage Strength	Description	Package Size, # Blisters	NDC #	WAC*
(100/50) fluticasone propionate 100 mcg/ salmeterol 50 mcg	Disposable, purple colored device (DISKUS) fitted with a dose counter, packaged within a purple colored, plastic coated, moisture protective foil pouch	60	0173-0695-00	$145.93
	Institutional pack of 1 disposable, purple colored device (DISKUS) fitted with a dose counter, packaged within a purple colored, plastic coated, moisture protective foil pouch	28	0173-0695-02	$90.00
(250/50) fluticasone propionate 250 mcg/ salmeterol 50 mcg	Disposable, purple colored device (DISKUS) fitted with a dose counter, packaged within a purple colored, plastic coated, moisture protective foil pouch	60	0173-0696-00	$181.31
	Institutional pack of 1 disposable, purple colored device (DISKUS) fitted with a dose counter, packaged within a purple colored, plastic coated, moisture protective foil pouch	14	0173-0696-04	$77.00
(500/50) fluticasone propionate 500 mcg/ salmeterol 50 mcg	Disposable, purple colored device (DISKUS) fitted with a dose counter, packaged within a purple colored, plastic coated, moisture protective foil pouch	60	0173-0697-00	$250.41
	Institutional pack of 1 disposable, purple colored device (DISKUS) fitted with a dose counter, packaged within a purple colored, plastic coated, moisture protective foil pouch	14	0173-0697-04	$125.51

*WAC = wholesale acquisition cost effective as of 11/18/2008. WAC is the listed price to wholesalers and warehousing chains, not including prompt pay, stocking or distribution allowances, or other discounts, rebates or charge backs.

Store at controlled room temperature, 20°-25°C (68°-77°F), in a dry place away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation device is not reusable. The device should be discarded 1 month after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads “0”), whichever comes first. Do not attempt to take the device apart.

Table 3. *Advair HFA*: Dosage Forms/ NDC / Wholesale Acquisition Cost

Dosage Strength Per Inhalation Ex Actuator	Description	Canister, # Metered Inhalations	NDC #	WAC*
45/21 Fluticasone propionate 45 mcg, salmeterol 21 mcg	12-g pressurized aluminum canister fitted with a dose counter per box of 1; purple actuator with light purple strapcap sealed in a plastic-coated, moisture-protective foil pouch, Patient Medication Guide	120	0173-0715-00 and 0173-0715-20	$145.93
115/21 Fluticasone propionate 115 mcg, salmeterol 21 mcg	12-g pressurized aluminum canister fitted with a dose counter per box of 1; purple actuator with light purple strapcap sealed in a plastic-coated, moisture-protective foil pouch, Patient Medication Guide	120	0173-0716-00 and 0173-0716-20	$181.31
230/21 Fluticasone propionate 230 mcg, salmeterol 21 mcg	12-g pressurized aluminum canister fitted with a dose counter per box of 1; purple actuator with light purple strapcap sealed in a plastic-coated, moisture-protective foil pouch, Patient Medication Guide	120	0173-0717-00 and 0173-0717-20	$250.41
*WAC = wholesale acquisition cost effective as of 11/18/2008. WAC is the listed price to wholesalers and warehousing chains, not including prompt pay, stocking or distribution allowances, or other discounts, rebates or charge backs. Store at 25°C (77°F); excursions permitted to 15°–30°C (59°-86°F). Exposure to temperatures above 120°F may cause bursting. Keep out of reach of children.				

4.3 AHFS or Other Drug Classification

DPS/AHFS DRUG CLASSIFICATION: DPS drug classification for fluticasone propionate is 68:04 and 12:12 for salmeterol xinafoate. *Advair* Products have not been classified by DPS/AHFS.

4.4 FDA Approved Indications

Advair Diskus

Asthma

Advair Diskus is indicated for the long-term, twice-daily, maintenance treatment of asthma in patients 4 years of age and older. Long-acting $beta_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in *Advair Diskus*, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe *Advair Diskus* for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies.

Important Limitations of Use:

- *Advair Diskus* is NOT indicated for the relief of acute bronchospasm.
- *Advair Diskus* is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting $beta_2$-agonists.

Chronic Obstructive Pulmonary Disease

Advair Diskus 250/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. *Advair Diskus* 250/50 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. *Advair Diskus* 250/50 twice daily is the only approved dosage for the treatment of COPD because an efficacy advantage of the higher strength *Advair Diskus* 500/50 over *Advair Diskus* 250/50 has not been demonstrated.

Important Limitations of Use: *Advair Diskus* is NOT indicated for the relief of acute bronchospasm.

Advair HFA

Asthma

Advair HFA is indicated for the long term, twice daily maintenance treatment of asthma in patients 12 years of age and older.

Long-acting beta$_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in *Advair HFA*, may increase the risk of asthma related death. Therefore, when treating patients with asthma, physicians should only prescribe *Advair HFA* for patients not adequately controlled on other asthma controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. *Advair HFA* is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting beta$_2$-agonists.

Advair HFA is NOT indicated for the relief of acute bronchospasm.

4.5 Use in Special Populations

Advair Diskus and *Advair HFA* have been assigned FDA Pregnancy Category C (i.e., there are no adequate and well-controlled studies in pregnant women).[61,68]

Prescribing Information

Pregnancy Category C. There are no adequate and well-controlled studies with Advair in pregnant women.[61,68]

Advair Diskus was teratogenic in mice and not in rats, although it lowered fetal weight in rats. Fluticasone propionate alone was teratogenic in mice, rats, and rabbits, and salmeterol alone was teratogenic in rabbits and not in rats. From the reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using combinations of fluticasone propionate and salmeterol when compared with toxicity data from the components administered separately.

Advair Diskus should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Advair Diskus: In the mouse reproduction assay, fluticasone propionate by the subcutaneous route at a dose approximately 3/5 the maximum recommended human daily inhalation dose (MRHD) on a mg/m^2 basis combined with oral salmeterol at a dose approximately 410 times the MRHD on a mg/m^2 basis produced cleft palate, fetal death, increased implantation loss, and delayed ossification. These observations are characteristic of glucocorticoids. No developmental toxicity was observed at combination doses of fluticasone propionate subcutaneously up to approximately 1/6 the MRHD on a mg/m^2 basis and oral doses of salmeterol up to approximately 55 times the MRHD on a mg/m^2 basis. In rats, combining fluticasone propionate subcutaneously at a dose equivalent to the MRHD on a mg/m^2 basis and an oral dose of salmeterol at approximately 810 times the MRHD on a mg/m^2 basis produced decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone. No such effects were seen when combining fluticasone propionate subcutaneously at a dose less than the MRHD on a mg/m^2 basis and an oral dose of salmeterol at approximately 80 times the MRHD on a mg/m^2 basis.

Fluticasone Propionate: Subcutaneous studies in the mouse at a dose less than the MRHD on a mg/m^2 basis and in the rat at a dose equivalent to the MRHD on a mg/m^2 basis revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose less than the MRHD on a mg/m^2 basis. However, no teratogenic effects were reported at oral doses up to approximately 5 times the MRHD on a mg/m^2 basis. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women

will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Salmeterol: No teratogenic effects occurred in rats at oral doses approximately 160 times the MRHD on a mg/m^2 basis. In Dutch rabbits administered oral doses approximately 50 times the MRHD based on comparison of the AUCs, salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at an oral dose approximately 20 times the MRHD based on comparison of the AUCs.

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose approximately 1,600 times the MRHD on a mg/m^2 basis. Extensive use of other beta agonists has provided no evidence that these class effects in animals are relevant to their use in humans.

4.6 Pharmacology

Pharmacology of Salmeterol

Salmeterol is a selective long-acting β_2-adrenergic agonist. *In vitro* studies and *in vivo* pharmacologic studies demonstrate that salmeterol is selective for β_2-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on β_1- and β_2-adrenoceptors. [88] *In vitro* studies show salmeterol to be at least 50 times more selective for β_2-adrenoceptors than albuterol. At clinical doses of 50 mcg, studies have shown salmeterol to occupy 4% of the available β_2-adrenoceptors in the lung.[77]

The pharmacologic effects of β_2-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic 3', 5' adenosine monophosphate (cyclic AMP).[77] Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from mast cells and other inflammatory cells.

Data suggests that salmeterol also exerts other non-bronchodilator effects that may contribute to its therapeutic effects in the treatment of asthma. [78] These effects include a beneficial effect on mucociliary clearance, [89] improvement in ciliary beat frequency, [90] [91] and protection of the airway epithelium from bacteria and their toxins.[92] [93] In addition, salmeterol has demonstrated anti-inflammatory effects including an inhibitory effect on mediator release, [94] [95] [96] [97] [98] [99] [100] [101] [102] inflammatory cell infiltration, [103] [104] [105,106] and eosinophil activation and degranulation. [107] [108,109] Salmeterol also has been shown to increase neutrophil apoptosis[110] and reduce antigen-induced increases in vascular permeability.[111] [112]

However, it is important to note that the clinical relevance of these effects in patients with asthma remains unknown since many of these effects have been determined by *in vitro* studies or animal models.

Pharmacology of Fluticasone Propionate

Corticosteroids have been demonstrated to be the most effective anti-inflammatory drugs developed to date for asthma.[2] Fluticasone propionate is a trifluorinated corticosteroid with potent anti-inflammatory activity. *In vitro* assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide.[113]

The precise mechanism of action of inhaled corticosteroids, like fluticasone propionate, in asthma is unknown. Corticosteroids have been associated with improvements in most of the pathophysiologic changes associated with asthma such as inhibition of multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) involved in the asthmatic response and the mediators they produce (e.g., histamine, eicosanoids, leukotrienes, and cytokines). In addition, evidence has suggested that ICS may have effects on reversing some aspects of airway remodeling. [74] [75] [76] Due to their broad effects on airway inflammation and its consequences, corticosteroids are regarded as the preferred treatment for persistent asthma in treatment guidelines.[2]

4.7 Pharmacokinetics/Pharmacodynamics

Systemic Bioavailability

Studies using oral dosing of labeled and unlabeled fluticasone propionate have demonstrated that the oral systemic bioavailability is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lungs is systemically absorbed.(114)

A pharmacokinetic study was conducted to determine the absolute and relative bioavailability of fluticasone propionate (FP) from *Advair HFA* and *Advair Diskus*.(115,116) A single-dose, single-blind, placebo-controlled, part-randomized, crossover study enrolled 15 healthy volunteers aged 18-50 years. Patients received a single dose of each of the following treatments with a minimum of five days between treatments: intravenous FP (0.5 mg/ml; total dose 1010 mcg), four inhalations of *Advair HFA* 230/21 (920 mcg FP, 84 mcg salmeterol), two inhalations *Advair Diskus* 500/50 (1000 mcg FP, 100 mcg salmeterol), and placebo *Diskus*. This study utilized liquid chromatography tandem mass spectrometry (LC-MS-MS) which has been reported to be a more sensitive and selective method of detection of FP compared with the previously used radioimmunoassay method.(117)

The systemic exposure of FP from *Advair HFA* and *Advair Diskus* was similar.(115,116) The absolute bioavailability of FP from *Advair HFA* and *Advair Diskus* expressed as a percentage of the intravenous formulation was 5.3% and 5.5%, respectively (Table 4).

Table 4. Absolute Bioavailability of FP*(115)

Parameter	*Advair HFA*	*Advair Diskus*
AUC_{last}, mean (%) (95% CI)	5.3 (3.6, 7.9)	5.5 (3.6, 7.9)
AUC∞ (pg•h/mL), mean (%) (95% CI)	6.3 (4.7, 8.5)	6 (4.5, 8.1)
AUC_{last} = area under the plasma concentration-time curve up to the last quantifiable concentration; AUC∞ = area under the plasma concentration-time curve to infinity; CI = confidence interval; * = expressed as a percentage of intravenous FP		

The relative bioavailability of FP was 96% (90% CI, 69-134%) comparing *Advair HFA* (mean AUC_{last} = 799 pg•h/mL) to *Advair Diskus* (mean AUC_{last} = 832 pg•h/mL). For salmeterol, the relative bioavailability was 82% (90% CI, 27-160%) higher from *Advair HFA* (mean AUC_{last} = 317 pg•h/mL) compared to *Advair Diskus* (mean AUC_{last} = 169 pg•h/mL) however the peak plasma concentrations of salmeterol were similar (mean C_{max} = 196 pg/mL and 223 pg/mL, respectively) and pharmacodynamic results (serum potassium, serum glucose and most measures of QTc interval) were comparable. The larger AUC_{last} for *Advair HFA* compared with *Advair Diskus* corresponding differences in the maximum observed salmeterol plasma concentration was explained by the more prolonged absorption observed in several subjects.

4.8 Contraindications

The use of *Advair Diskus* is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
- Severe hypersensitivity to milk proteins.(68)

Advair HFA is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.(61) Hypersensitivity to any of the ingredients of these preparations contraindicates their use.

4.9 Warnings/Precautions

Long-acting beta$_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in *Advair*, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe *Advair* for patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease

severity clearly warrants initiation of treatment with 2 maintenance therapies. Data from a large placebo-controlled US study that compared the safety of salmeterol (Serevent® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo).

Refer to Enclosed Prescribing Information.

4.10 Adverse Events

Refer to Enclosed Prescribing Information.

4.11 Other Clinical Considerations

Refer to Enclosed Prescribing Information.

4.12 Drug/Food/Disease Interactions

Refer to Enclosed Prescribing Information.

4.13 Dosing and Administration

Dosage And Administration of Advair Diskus in Asthma

Advair Diskus should be administered twice daily every day by the orally inhaled route only.[68] After inhalation, the patient should rinse the mouth with water without swallowing.

More frequent administration or a higher number of inhalations (more than 1 inhalation twice daily) of the prescribed strength of *Advair Diskus* is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. Patients using *Advair Diskus* should not use additional long-acting beta$_2$-agonists for any reason.

If symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

Advair Diskus is available in 3 strengths, *Advair Diskus* 100/50, *Advair Diskus* 250/50, and *Advair Diskus* 500/50, containing 100, 250, and 500 mcg of fluticasone propionate, respectively, and 50 mcg of salmeterol per inhalation.

Adult and Adolescent Patients 12 Years of Age and Older:

For patients 12 years of age and older, the dosage is 1 inhalation twice daily (morning and evening, approximately 12 hours apart).

The recommended starting dosages for *Advair Diskus* for patients 12 years of age and older are based upon patients' asthma severity. For patients not currently on inhaled corticosteroids whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, or patients inadequately controlled on an inhaled corticosteroid, the recommended starting dosage is *Advair Diskus* 100/50 or 250/50 twice daily.

The maximum recommended dose is *Advair Diskus* 500/50 twice daily.

For all patients it is desirable to titrate to the lowest effective strength after adequate asthma stability is achieved.

Improvement in asthma control following inhaled administration of *Advair Diskus* can occur within 30 minutes of beginning treatment, although maximum benefit may not be achieved for 1 week or longer after starting treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dose after 2 weeks of therapy, replacing the current strength of *Advair Diskus* with a higher strength may provide additional improvement in asthma control.

If a previously effective dosage regimen of *Advair Diskus* fails to provide adequate improvement in asthma control, the therapeutic regimen should be reevaluated and additional therapeutic options (e.g., replacing

the current strength of *Advair Diskus* with a higher strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids) should be considered.

Pediatric Patients 4 to 11 Years of Age:

For patients with asthma aged 4 to 11 years who are symptomatic on an inhaled corticosteroid, the dosage is 1 inhalation of *Advair Diskus* 100/50 twice daily (morning and evening, approximately 12 hours apart).

Dosing and Administration of Advair HFA in Asthma

Advair HFA should be administered only by the orally inhaled route in patients 12 years of age and older.[61] *Advair HFA* should not be used for transferring patients from systemic corticosteroid therapy. *Advair HFA* is not indicated for use in patients under 12 years of age or in patients with chronic obstructive pulmonary disease (COPD).

Long-acting beta$_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in *Advair HFA*, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe *Advair HFA* for patients not adequately controlled on other asthma controller medications (e.g., low- to medium dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. *Advair HFA* is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting beta$_2$-agonists.

Advair HFA should be administered as 2 inhalations twice daily every day. More frequent administration (more than twice daily) or a higher number of inhalations (more than 2 inhalations twice daily) of the prescribed strength of *Advair HFA* is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. The safety and efficacy of *Advair HFA* when administered in excess of recommended doses have not been established.

If symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

Patients who are receiving *Advair HFA* twice daily should not use additional salmeterol or other inhaled, long-acting beta$_2$-agonists (e.g., formoterol) for prevention of exercise-induced bronchospasm (EIB) or for any other reason.

Adult and Adolescent Patients 12 Years of Age and Older

For patients 12 years of age and older, the dosage for *Advair HFA* is 2 inhalations twice daily (morning and evening, approximately 12 hours apart).[61]

Advair HFA is available in 3 strengths: *Advair HFA* 45/21, *Advair HFA* 115/21, and *Advair HFA* 230/21. Each contains 45, 115, and 230 mcg of fluticasone propionate, respectively, and 21 mcg of salmeterol per inhalation.

The recommended starting dosages for *Advair HFA* are based upon patients' current asthma therapy. For patients not adequately controlled on an inhaled corticosteroid, Table 5 provides the recommended starting dosage. For patients not currently on inhaled corticosteroids, whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, the recommended starting dosage is 2 inhalations of *Advair HFA* 45/21 or *Advair HFA* 115/21 twice daily.

The maximum recommended dosage is 2 inhalations of *Advair HFA* 230/21 twice daily. For all patients it is desirable to titrate to the lowest effective strength after adequate asthma stability is achieved.

Table 5. Recommended Dosages of *Advair HFA* for Patients Not Adequately Controlled on Inhaled Corticosteroids

Current Daily Dose of Inhaled Corticosteroid		Recommended Strength of *Advair HFA* (2 inhalations twice daily)
Beclomethasone dipropionate HFA inhalation aerosol	≤160 mcg	45/21
	320 mcg	115/21
	640 mcg	230/21
Budesonide inhalation powder	≤400 mcg	45/21
	800-1,200 mcg	115/21
	1,600 mcg*	230/21
Flunisolide CFC inhalation aerosol	≤1,000 mcg	45/21
	1,250-2,000 mcg	115/21
Flunisolide HFA inhalation aerosol	≤320 mcg	45/21
	640 mcg	115/21
Fluticasone propionate HFA inhalation aerosol	≤176 mcg	45/21
	440 mcg	115/21
	660-880 mcg*	230/21
Fluticasone propionate inhalation powder	≤200 mcg	45/21
	500 mcg	115/21
	1,000 mcg*	230/21
Mometasone furoate inhalation powder	220 mcg	45/21
	440 mcg	115/21
	880 mcg	230/21
Triamcinolone acetonide inhalation aerosol	≤1,000 mcg	45/21
	1,100-1,600 mcg	115/21
* *Advair HFA* should not be used for transferring patients from systemic corticosteroid therapy.		

Improvement in asthma control following inhaled administration of *Advair HFA* can occur within 30 minutes of beginning treatment. Maximum benefit may not be achieved for 1 week or longer after starting treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, replacing the current strength of *Advair HFA* with a higher strength may provide additional improvement in asthma control. If a previously effective dosage regimen of *Advair HFA* fails to provide adequate improvement in asthma control, the therapeutic regimen should be re-evaluated and additional therapeutic options, e.g., replacing the current strength of *Advair HFA* with a higher strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be considered.

Pediatric Use

The safety and efficacy of *Advair HFA* in children under 12 years of age have not been established.[61]

Geriatric Use

In studies where geriatric patients (65 years of age or older) have been treated with *Advair HFA*, efficacy and safety did not differ from that in younger patients. Based on available data for *Advair HFA* and its active components, no dosage adjustment is recommended.[61]

Dosage and Administration of Advair Diskus in COPD

The recommended dosage for patients with COPD is 1 inhalation of *Advair Diskus* 250/50 twice daily (morning and evening, approximately 12 hours apart).[68]

If shortness of breath occurs in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

4.14 Co-prescribed/Concomitant Therapies

Refer to Enclosed Prescribing Information.

4.15 Product Comparisons

Table 6. Comparison of Available Inhaled Corticosteroid Plus Long-Acting Beta$_2$-Agonist Fixed Dose Combination Products

	Advair Diskus	***Advair HFA***	**Symbicort**
Active Ingredients	Fluticasone Propionate Salmeterol	Fluticasone Propionate Salmeterol	Budesonide Formoterol Fumarate Dihydrate
Formulation	Dry Powder Inhaler, fitted with a dose counter	Metered-Dose Inhaler, fitted with a dose counter	Metered-Dose Inhaler, fitted with a dose counter
Strengths Available	100/50, 250/50, 500/50	45/21, 115/21, 230/21	80/4.5, 160/4.5
Indications	Asthma (Patients ≥4 years) COPD (airflow obstruction and reducing exacerbations)	Asthma (Patients ≥12 years)	Asthma (Patients ≥12 years) COPD (airflow obstruction)
Dosing	1 inhalation BID*†	2 inhalations BID	2 inhalations BID‡

*For patients aged 4 to 11 years who are symptomatic on an inhaled corticosteroid the dosage is 1 inhalation of *Advair Diskus* 100/50 twice daily.

†*Advair Diskus* 250/50 mcg twice daily is the only approved dosage for the treatment of COPD.

BID=twice daily

‡Symbicort 160/4.5 two inhalations BID is the only approved dosage for the treatment of COPD

5. EFFICACY AND SAFETY TRIALS (FDA APPROVED INDICATIONS)

5.1 Pivotal Efficacy and Safety Trials with *Advair Diskus* in Adults and Adolescents with Asthma

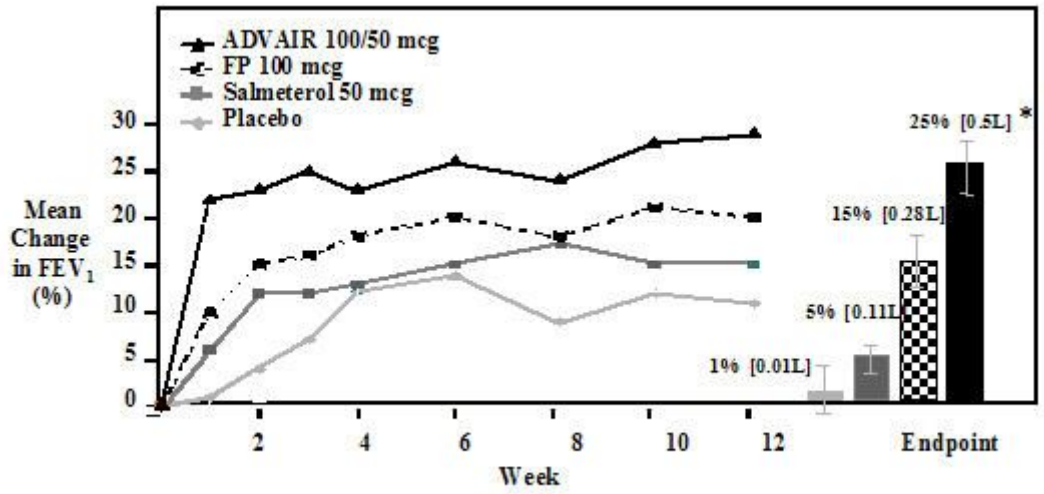
A pivotal, multicenter, randomized, double-blind, parallel group, placebo-controlled trial conducted in the United States (U.S.) compared the efficacy and safety of *Advair Diskus* 100/50 with FP 100 mcg alone, and salmeterol xinafoate 50 mcg alone. [7] The study consisted of 335 patients with mild to moderate asthma [mean forced expiratory volume in 1 second (FEV_1) = 64% of predicted] and a history of treatment with either inhaled corticosteroids (70%) or salmeterol (30%). Previous inhaled corticosteroid use was restricted to beclomethasone dipropionate (252-420 mcg/day), triamcinolone acetonide (600-1000 mcg/day), flunisolide (1000 mcg/day), or FP inhalation aerosol (176 mcg/day). After a 2-week run-in, patients were randomized to twice daily treatment with either placebo, *Advair Diskus* 100/50, salmeterol 50 mcg via *Diskus*, or FP 100 mcg via *Diskus* for 12 weeks. All patients received as-needed albuterol via metered-dose inhaler (MDI).

Primary efficacy measures included FEV_1 area under the curve (AUC) during 12-hour serial pulmonary function tests after week 1 of treatment, morning (AM) pre-dose FEV_1 at endpoint and the probability of remaining in the study over time (withdrawals due to lack of efficacy). Secondary efficacy measures included AM and evening (PM) peak expiratory flow (PEF). Other efficacy measures included daily patient-rated diary symptom scores, albuterol use, and nighttime awakenings.

At endpoint, mean change from baseline in AM pre-dose FEV_1 for patients receiving placebo, salmeterol, FP, and *Advair Diskus* 100/50 were 0.01 L (1%), 0.11 L (5%), 0.28 L (15%), and 0.51 L (25%), respectively ($P \leq 0.003$, *Advair Diskus* vs. placebo, salmeterol, FP) (Figure 1). On treatment day 1, the mean percent change in FEV_1 at 30 minutes was 8.66%, 18.2%, 8.23%, and 18.97% for placebo, salmeterol, FP, and *Advair Diskus* 100/50, respectively. On day 1, maximum effects were seen within 3 hours and maintained over 12 hours. Further improvements were observed with no diminution in effect on treatment week 12.

Mean FEV_1 AUC at week 1 values were 2.56 L/hr, 4.90 L/hr, 3.58 L/hr, and 7.67 L/hr for placebo, salmeterol, FP, and *Advair Diskus* 100/50, respectively ($P < 0.001$, *Advair Diskus* vs. placebo, salmeterol, FP). No differences were seen between groups previously treated with inhaled corticosteroids or salmeterol.

Figure 1. Mean Change from Baseline in Morning Pre-dose FEV_1



*Differs from FP 100 mcg, salmeterol, placebo at endpoint $P \leq 0.008$

After 12 weeks of treatment, the percent of patients that withdrew due to lack of efficacy were 49%, 35%, 11%, and 3% for placebo, salmeterol, FP, and *Advair Diskus* 100/50, respectively ($P \leq 0.047$*Advair Diskus* vs. placebo, salmeterol, FP).

In addition, improvements in AM and PM PEF were seen in patients receiving *Advair Diskus* 100/50. At endpoint, the group treated with *Advair Diskus* 100/50 had a mean change in AM PEF of 52.5 L/min compared with –23.7 L/min, -1.7 L/min, 17.3 L/min in the placebo, salmeterol, FP groups, respectively ($P < 0.001$, *Advair Diskus* vs. placebo, salmeterol, FP). Furthermore, the changes in PM PEF were –13.3 L/min, –7.4 L/min, 18 L/min and 35 L/min for the groups treated with placebo, salmeterol, FP, and *Advair Diskus* 100/50, respectively ($P \leq 0.012$, *Advair Diskus* vs. placebo, salmeterol, FP). Other efficacy results are listed in Table 7.

Table 7. Mean Change From Baseline At Endpoint In Other Efficacy Parameters

	***Advair Diskus* 100/50 (n=87)**	**FP 100 mcg (n=85)**	**Salmeterol 50 mcg (n=86)**	**Placebo (n=77)**
Asthma Symptom Score				
Baseline	1.5	1.6	1.8	1.8
Mean Change	-0.7*†‡	-0.2*	-0.1*	0.4
% Of Days With No Asthma Symptoms				
Baseline	25.2	19.4	12.6	15.8
Mean Change	22.6*†	7.2	8.0*	-3.8
% Of Nights With No Awakenings				
Baseline	91.7	91.3	91.6	89.9
Mean Change	4.6*†	2.4*	-5.3*	-16.5
Albuterol Use (puffs/day)				
*$P \leq 0.013$ vs. placebo; †$P \leq 0.023$ vs. salmeterol; ‡$P \leq 0.025$ vs. FP				

	***Advair Diskus* 100/50 (n=87)**	**FP 100 mcg (n=85)**	**Salmeterol 50 mcg (n=86)**	**Placebo (n=77)**
Baseline	3.1	3.1	3.3	3.2
Mean Change	-1.9*†‡	-0.4*	-0.3*	1.7
*$P \leq 0.013$ vs. placebo; †$P \leq 0.023$ vs. salmeterol; ‡$P \leq 0.025$ vs. FP				

Advair Diskus 100/50 (n=92) was generally well-tolerated over 12 weeks of treatment. The most commonly reported (≥2%) drug-related adverse events following the use of *Advair Diskus* were throat irritation (4%), hoarseness/dysphonia (3%), candidiasis, unspecified site (3%), and headache (2%). There was no evidence of any additional safety concerns with *Advair Diskus* compared with use of FP alone or salmeterol alone. Four patients withdrew from the study due to adverse events; however, these adverse events were considered by the investigator to be unrelated to any study drug.

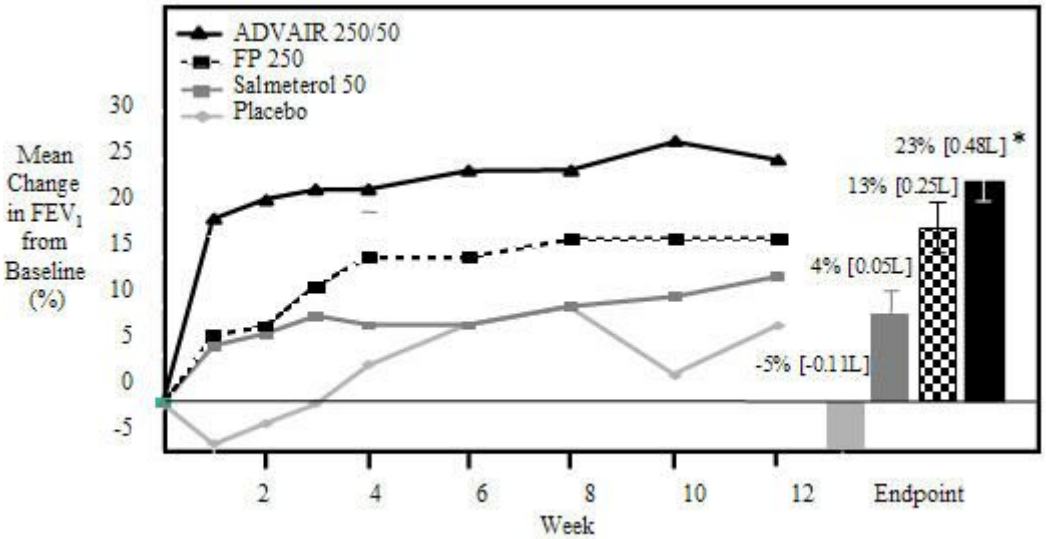
A pivotal, multicenter, randomized, double-blind, parallel group, placebo-controlled, 12-week trial conducted in the U.S. compared the efficacy of *Advair Diskus*, salmeterol, and FP. [8] The study evaluated 349 adult and adolescent patients with mild to moderate persistent asthma [mean FEV_1 = 66-68% of predicted] previously treated with inhaled corticosteroids. Prior to randomization, patients were receiving treatment with beclomethasone dipropionate (462-672 mcg/day), triamcinolone acetonide (1100-1600 mcg/day), flunisolide (1250-2000 mcg/day), or FP (440 mcg/day).

After a 2-week run-in period, use of inhaled corticosteroids was discontinued, and patients were randomized to twice daily treatment with either salmeterol 50 mcg via *Diskus*, FP 250 mcg via *Diskus*, *Advair Diskus* 250/50, or placebo. All patients received as-needed albuterol via metered-dose inhaler (MDI).

Primary efficacy measures included FEV_1 area under the curve (AUC) during 12-hour serial pulmonary function tests after week 1 of treatment, morning (AM) pre-dose FEV_1 at endpoint, and the probability of remaining in the study over time (withdrawals due to lack of efficacy).

At endpoint, patients treated with *Advair Diskus* 250/50 had a significantly higher mean change from baseline in AM pre-dose FEV_1 compared with patients receiving placebo, salmeterol, and FP (Figure 2). Mean FEV_1AUC at week 1 values were -0.09 L/hr, 3.78 L/hr, 2.01 L/hr, and 6.71 L/hr for placebo, salmeterol, FP, and *Advair Diskus* 250/50, respectively ($P < 0.025$, *Advair Diskus* vs. placebo, salmeterol, FP).

Figure 2. Mean Change from Baseline in Morning Pre-dose FEV_1



*Differs from FP 250, salmeterol, placebo at endpoint $P \leq 0.003$

The percent of patients that withdrew due to lack of efficacy were 62%, 38%, 22%, and 4% in the groups receiving placebo, salmeterol, FP, and *Advair Diskus* 250/50, respectively ($P \leq 0.003$, *Advair Diskus* vs. placebo, salmeterol, FP).

Improvements in secondary and other efficacy measures were also seen in patients treated with *Advair Diskus* 250/50 (Table 8).

Table 8. Mean Change From Baseline At Endpoint in Secondary and Other Efficacy Parameters

	***Advair Diskus* 250/50 (n=81)**	**FP 250 mcg (n=81)**	**Salmeterol 50 mcg (n=84)**	**Placebo (n=90)**
AM PEF (L/min)				
Baseline	367	374	372	373
Mean Change	53.5*†‡	15.2*	-11.6	-14.1
PM PEF (L/min)				
Baseline	388	388	393	396
Mean Change	45.4*†‡	7.9*	-13.7	-15.8
Asthma Symptom Score				
Baseline	1.4	1.6	1.6	1.6
Mean Change	-0.8*†‡	-0.4*	0.1*	0.4
% of Days with No Symptoms				
Baseline	26.5	23.5	19.2	24.1
Mean Change	33.8*†‡	15.4*	2.1	-7.9
% of Nights with No Awakenings				
Baseline	90.7	90.5	89.7	89.1
Mean Change	7.2*†‡	2.8*	-8	-12
Albuterol Use (puffs/day)				
Baseline	3.5	3.2	3.8	3.8
Mean Change	-2.3*†‡	-0.9*	0*	0.9
*$P \leq 0.036$ vs placebo; †$P \leq 0.003$ vs salmeterol; ‡$P \leq 0.015$ vs FP				

Each treatment group was generally well-tolerated over the 12-week study period. The most commonly occurring drug-related adverse events (≥2%) were candidiasis (unspecified sites and oropharyngeal) and cough. No serious drug-related adverse events were reported. No clinically significant differences were noted with respect to morning plasma cortisol abnormalities or response to synthetic corticotropin stimulation testing.

Advair Diskus 500/50 versus FP 500 mcg + Salmeterol 50 mcg versus FP 500 mcg Alone

A pivotal, multicenter, randomized, double-blind, double-dummy, parallel-group comparison of *Advair Diskus* versus concurrent use of salmeterol and FP versus FP alone was conducted in 503 adolescents and adults with reversible airways obstruction [mean FEV_1 = 71-72% of predicted] in Germany, France and the Netherlands. [9] During a 2-week run-in period, patients continued treatment with their current inhaled corticosteroid (beclomethasone dipropionate 1260-1680 mcg/day, budesonide 1500-2000 mcg/day, flunisolide 1500-2000 mcg/day or FP 750-1000 mcg/day). Patients discontinued therapy with their current inhaled corticosteroid and were randomized to twice daily treatment with either *Advair Diskus* 500/50, salmeterol 50 mcg via *Diskus* plus FP 500 mcg via *Diskus* or FP 500 mcg via *Diskus* alone for 28 weeks.

All patients received as-needed albuterol administered either by Diskhaler® or metered-dose inhaler (MDI). The primary efficacy parameter was morning (AM) peak expiratory flow (PEF). Efficacy measurements were collected during the first 12 weeks of therapy. Treatment was continued an additional 12 weeks to gather safety information for a total of 28 weeks of treatment.

During weeks 1-12, the mean changes from baseline in AM PEF were 35 L/min, 33 L/min, and 15 L/min for *Advair Diskus* 500/50, salmeterol plus FP, and FP alone, respectively ($P < 0.001$, *Advair Diskus* vs. FP alone). *Advair Diskus* 500/50 and concurrent therapy were equivalent based on 90% and 95% confidence limits for AM peak expiratory flow rate (PEFR), which were within +/-15 L/min.

Improvements in secondary efficacy measures were observed in the group receiving *Advair Diskus* 500/50, concurrent therapy, and FP (Table 9).

Table 9. *Advair Diskus* 500/50 versus FP 500 mcg +/- Salmeterol 50 mcg: Secondary Endpoints

	***Advair* 500/50 (n=167)**	**FP 500 + Salmeterol 50 (n=171)**	**FP 500 (n=165)**	***Advair* 500/50 vs FP 500***
PM PEF (L/min)				
Baseline	379	366	368	
Mean change from baseline at Week 12	28	23	9	$P < 0.001$
Median % of Days With No Symptoms				
Baseline	0	0	0	
Over Weeks 1-12	24	27	7	$P < 0.023$
Median % of Nights With No Symptoms				
Baseline	14	14	29	
Over Weeks 1-12	73	66	57	NS
Median % of Days with No Albuterol Use				
Baseline	0	0	0	
Over Weeks 1-12	50	45	13	$P < 0.023$
Clinic FEV_1 (L)				
Baseline	2.38	2.29	2.25	
Mean change from baseline at Week 12	0.22	0.17	0.13	NS
*No significant differences between *Advair Diskus* 500/50 and FP + salmeterol				

All treatment groups were generally well-tolerated over 28 weeks. Adverse events with *Advair Diskus* 500/50 did not increase in severity or frequency compared with FP alone. The most commonly reported drug-related adverse events (≥2%) following the use of *Advair Diskus* 500/50 (n=167) were breathing disorders (3%), asthma (2%), hoarseness/dysphonia (2%), and headache (2%). No differences were observed in change in serum cortisol levels or 24-hour urinary cortisol between groups.

5.2 Pivotal Efficacy and Safety Trials with *Advair Diskus* in Children with Asthma

Clinical Trials in Children

Advair Diskus 100/50 vs. Concurrent Salmeterol 50 mcg and Fluticasone Propionate 100 mcg

Van den Berg et al demonstrated the equivalence of *Advair Diskus* 100/50 twice daily with the concurrent use of salmeterol via *Diskus* 50 mcg twice daily plus FP via *Diskus* 100 mcg twice daily. This study enrolled 257 children 4 to 11 years of age with asthma in a 12-week, randomized, double-blind, double-dummy, parallel-group trial. [118] The study population was symptomatic on their current inhaled corticosteroid (400-500 mcg of beclomethasone dipropionate, budesonide, or flunisolide or 200-250 mcg of FP daily). Mean baseline PEF and FEV_1 were 100% and 84%-86% of predicted, respectively. After a 2-week run-in period, the patients (mean age 7.6 years) were randomized to treatment. All patients received as-needed albuterol. The primary efficacy measure was morning PEF.

Over weeks 1-12, the adjusted mean change from baseline in morning PEF was 33 L/min and 28 L/min for *Advair Diskus* 100/50 and concurrent FP plus salmeterol, respectively. The difference between the groups was –5 L/min (90% confidence limit –10 to +0 L/min), which met the predefined criteria for equivalence.

No statistically significant difference was observed between *Advair Diskus* 100/50 and concurrent salmeterol plus FP therapy for the secondary efficacy measures (Table 10).

Table 10. *Advair Diskus* 100/50 vs FP 100 mg Plus Salmeterol 50 mcg in Children: Secondary Endpoints

	Advair Diskus **(n=125)**	**Salmeterol + FP (n=132)**
PM PEF weeks 1-12 (adjusted mean change from baseline)	29 L/min	25 L/min
FEV_1 (adjusted mean change from baseline at week 12)*	0.21 L	0.13 L
% patients with median daytime symptom score of zero	Baseline: 24% Weeks 1-12: 61%	Baseline: 20% Weeks 1-12: 59%
% patients with median nighttime symptom score of zero	Baseline: 49% Weeks 1-12: 78%	Baseline: 51% Weeks 1-12: 76%
Median % nights with no albuterol	Baseline: 86% Weeks 1-12: 98%	Baseline: 100% Weeks 1-12: 96%
*FEV_1 values were obtained when possible *Advair Diskus* (n=105); Salmeterol + FP (n=107)		

The most common drug-related adverse events (≥2%) for both groups were candidiasis of mouth/throat (2% and 2%, respectively), malaise and fatigue (<1% and 2%, respectively), candidiasis (unspecified site) (2% and 0%, respectively), aggression and hostility (<1% and 2%, respectively), and lower respiratory tract disorder (<1% and 2%, respectively). No statistically significant differences were noted in the incidence of adverse events between groups. During the study period, treatment groups were similar for mean serum cortisol concentrations, and no differences were seen in the frequency of serum cortisol abnormalities.

Advair Diskus 100/50 Versus Fluticasone Propionate (FP) 100 mcg Alone

A 12-week, double-blind, randomized, parallel-group study compared the safety of *Advair Diskus* 100/50 twice daily with FP 100 mcg via Diskus twice daily in 203 children 4 to 11 years old who were symptomatic while receiving an ICS. [16] Entry criteria required a forced expiratory volume in one second [FEV_1] (6-11 years old) or morning peak expiratory flow [AM PEF] (4-5 years old) 50% to 95% of predicted and reversibility ≥12% after albuterol 180-360 mcg. Eligible patients continued baseline ICS therapy and were given albuterol metered-dose inhaler for rescue use during a 2-week run-in phase. At the end of the run-in phase, patients who met the following randomization criteria continued into the double-blind treatment phase: (1) an FEV_1 (6-11 years old) or AM PEF (4-5 years old) 50% to 95% of predicted, (2) a daytime symptom score of at least 1 on 3 or more days or rescue albuterol use on 3 or more days within the 7 days prior to randomization, and (3) at least 70% or greater compliance with diary card completion. The safety assessments included adverse events, clinical hematology and chemistry laboratory tests, 24-hour urinary cortisol excretion, 12-lead ECGs, vital signs, physical and oropharyngeal examination, and asthma exacerbations/worsening asthma. Patient demographics and pulmonary function were comparable at baseline across the treatment groups (Table 11). FP was the most commonly used ICS prior to randomization in each treatment group with a mean daily dose of 166-167 mcg.

Table 11. Patient Demographics [119]

	Advair Diskus **100/50**		**FP 100 mcg**	
Age, years	**4-5**	**6-11**	**4-5**	**6-11**
Number, n	21	80	19	83
Gender: Female/Male	8/13	24/56	9/10	33/50
Ethnicity: Caucasian	57%	70%	84%	69%
African American	24%	23%	0	19%
Asian	5%	3%	0	1%
American Hispanic	14%	5%	16%	11%
Mean FEV_1 % predicted, 6-11 years	---	80.9	---	80
Mean PEF% predicted, 4-5 years	83.9	---	89.4	---
Mean duration of asthma, years	5.3		5.1	

The incidence of adverse events reported were generally similar between treatment groups (Table 12). Thirteen percent of patients receiving *Advair Diskus* and 9% of patients receiving FP experienced at least one adverse event which was considered by the investigator to be drug-related. Of the patients treated with *Advair Diskus* who experienced drug-related adverse events, two withdrew prematurely from the

study due to chest symptoms and sleeplessness. None of the patients treated with FP were withdrawn prematurely due to adverse events.

Table 12. Adverse Events Reported or Observed in ≥5% of Patients receiving *Advair Diskus* (16)

Adverse Event,% reported	***Advair Diskus* 100/50 (n=101)**	**FP 100 (n=102)**
Headache	20%	20%
Upper Respiratory Tract Infection	10%	17%
Fever	5%	13%
Throat Irritation	8%	7%
Gastrointestinal discomfort and pain	7%	5%
Nausea and vomiting	5%	3%

The values for 24-hour urinary cortisol excretion at baseline and after 12 weeks of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol excretion was also similar between the two groups, and no subject in either treatment group had a value below the lower limit of the normal range.

Hematology and chemistry values were in the normal range for all but 3 patients in each group. For all patients in both groups at 12 weeks, ECGs, mean heart rate, QTc intervals, and vital signs were considered normal or comparable to baseline values, as well as similar between groups.

The incidence of asthma exacerbations (3% and 8%) and withdrawals due to an asthma exacerbation (2% and 5%) were lower in the group treated with *Advair* compared with FP.

5.3 Pivotal Efficacy and Safety Trials with *Advair Diskus* in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Clinical Information

U.S. Pivotal Study

In a randomized, double-blind, placebo-controlled, parallel-group study, the efficacy and safety of *Advair Diskus* 250/50 in the treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis was evaluated in a comparison with fluticasone propionate (FP) 250 mcg, salmeterol 50 mcg, and placebo. (45,120) All treatments were administered via the Diskus® device. This study included 723 patients 40 years of age and older with a current or prior cigarette smoking history of at least 20 pack-years, and with an American Thoracic Society (ATS) defined diagnosis for COPD.(121) Patients had dyspnea and a history of cough productive of sputum on most days for at least 3 months of the year for at least two years that was not attributable to another disease process. Patients were required to have airflow obstruction as demonstrated by a FEV_1/forced vital capacity (FVC) ratio of ≤70%. Patients were also required to have an FEV_1 greater than 0.70 L and less than 65% of predicted or an FEV_1 less than 0.70 L and 40%-65% of predicted.

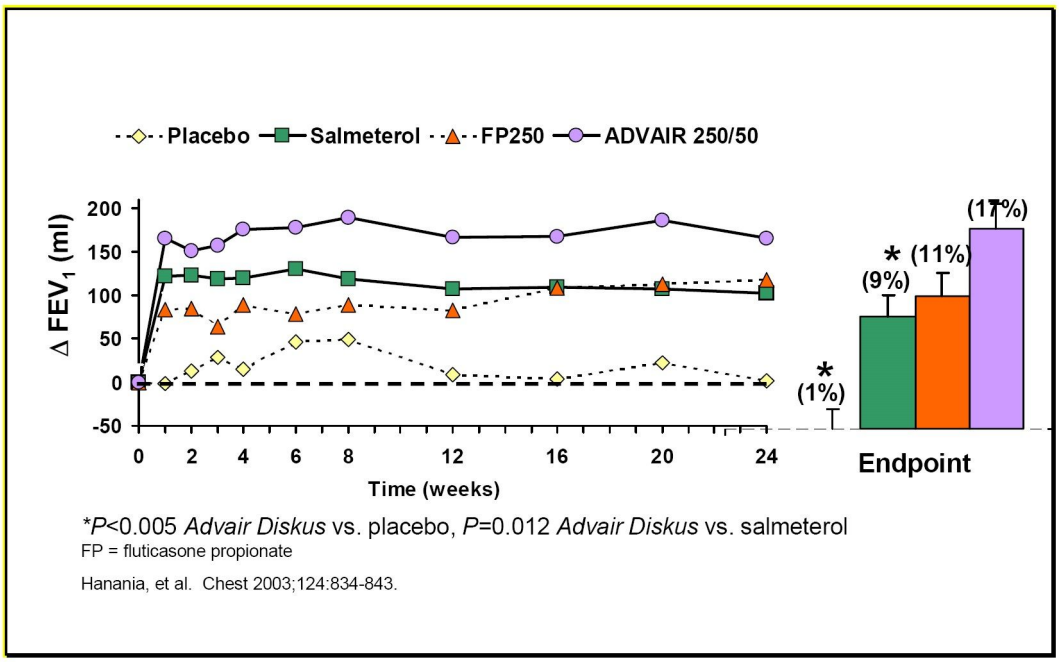
The study design included a two-week, single blind, run-in period, followed by a 24-week treatment phase. During the run-in and treatment phases, all concurrent use of inhaled and oral corticosteroids and bronchodilators (sympathomimetic or anticholinergic) was discontinued. Theophylline was permitted if the dose had been stable for at least one month, and doses could be adjusted to maintain a therapeutic level. Albuterol via pressurized metered dose inhaler (MDI) or nebulizer was provided for symptomatic relief. The primary efficacy endpoints were: 1) change from baseline in morning pre-dose, pre-bronchodilator FEV_1 between *Advair Diskus* and salmeterol (to assess the contribution of FP), and 2) change from baseline in two-hour post-dose FEV_1 between *Advair Diskus* and FP (to assess the contribution of salmeterol).

Baseline patient demographics were similar among the treatment groups. The mean age was approximately 64 years, on average 43-51% were current smokers, and the mean FEV_1 was approximately 42%. At baseline, the most frequently used COPD medications were anticholinergics (24-35%), inhaled corticosteroids (20-31%), salmeterol (11-17%), and theophylline (10-12%).

Patients treated with *Advair Diskus* 250/50 experienced a significantly greater improvement in pre-dose FEV_1 from Baseline to Endpoint (165 mL) compared with those treated with salmeterol 50 mcg (91 mL,

P =0.012). This demonstrated a significant contribution of fluticasone propionate (FP) 250 mcg to the efficacy of *Advair Diskus* 250/50. The improvement in morning pre-dose FEV_1 associated with *Advair Diskus* 250/50 was also significantly better than that seen with placebo (1 mL, $P \leq 0.005$). These increases in pre-dose FEV_1 corresponded with mean percent changes from Baseline of 17% and 9% for *Advair Diskus* 250/50 and salmeterol 50 mcg groups, respectively. Pre-dose FEV_1 values remained consistent throughout the 24 weeks of the treatment phase (See Figure 3 below).

Figure 3. Mean Change from Baseline of Pre-dose FEV_1 (mL)

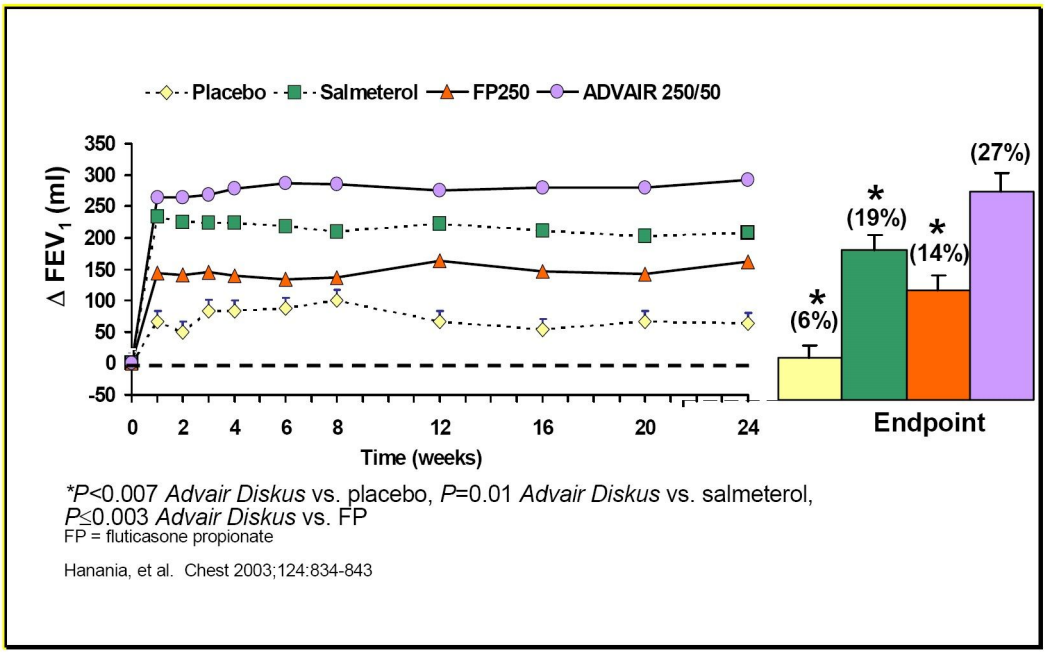


**P*<0.005 *Advair Diskus* vs. placebo, *P*=0.012 *Advair Diskus* vs. salmeterol
FP = fluticasone propionate
Hanania, et al. Chest 2003;124:834-843.

A greater increase in pre-dose FEV_1 was seen at Week 1 with *Advair Diskus* 250/50 (165 mL) compared with salmeterol 50 mcg (122 mL, *P*=0.026); this supported an early contribution of FP 250 mcg to the efficacy of *Advair Diskus*.

A significant improvement in two-hour post-dose FEV_1 from Baseline to Endpoint was observed in patients treated with *Advair Diskus* 250/50 (281 mL) compared to those treated with FP 250 mcg (147 mL, *P*<0.001). This demonstrated a significant contribution of salmeterol 50 mcg to the efficacy of *Advair Diskus* 250/50. The improvement in two-hour post-dose FEV_1 associated with *Advair Diskus* 250/50 was also significantly better than that seen with salmeterol 50 mcg (200 mL, *P*=0.01) or placebo (58 mL, *P*<0.001). These increases in two-hour post-dose FEV_1 corresponded with mean percent changes from Baseline of 27% for *Advair Diskus*, 14% for FP 250 mcg, 19% for salmeterol, and 6% for placebo. Two-hour post-dose FEV_1 values remained consistent throughout the 24 weeks of the treatment phase (See Figure 4 below).

Figure 4. Mean Change from Baseline of Two-hour Post-Dose FEV_1 (mL)



**P*<0.007 *Advair Diskus* vs. placebo, *P*=0.01 *Advair Diskus* vs. salmeterol, *P*≤0.003 *Advair Diskus* vs. FP
FP = fluticasone propionate

Hanania, et al. Chest 2003;124:834-843

Secondary endpoints included assessment of symptoms using the Baseline/Transition Dyspnea Index (BDI/TDI) [122] and the Chronic Bronchitis Symptom Questionnaire (CBSQ), [123] COPD exacerbations (severity, time to first exacerbation, withdrawals due to exacerbation), morning peak expiratory flow, rescue albuterol use, nighttime awakenings requiring albuterol, quality of life assessed by the Chronic Respiratory Disease Questionnaire (CRDQ). [124]

When compared with placebo, *Advair Diskus* 250/50 provided statistically significant improvements in all secondary endpoints except exacerbations. *Advair Diskus* 250/50 was also statistically significantly better than salmeterol 50 mcg for morning peak expiratory flow, and better than FP 250 mcg for morning peak expiratory flow and rescue albuterol use. The improvement from Baseline in TDI, CBSQ, and CRDQ for *Advair Diskus* 250/50 met or exceeded the MCIC in each assessment. However, differences between *Advair Diskus* 250/50 and other treatment groups for TDI, CBSQ, and CRDQ at Endpoint did not exceed the MCIC.

The most common adverse events (≥5%) reported among patients receiving *Advair Diskus* included headache, candidiasis mouth/throat, musculoskeletal pain, throat irritation, viral respiratory infections, and hoarseness/dysphonia. At selected sites, the short cosyntropin stimulation test was conducted. The incidence of abnormal cosyntropin stimulation values at Endpoint (week 24 or discontinuation visit) was similar for the patients taking an inhaled corticosteroid (ICS) (i.e., *Advair Diskus* and FP, nine patients) compared with those not taking an ICS (i.e., salmeterol and placebo, six patients). The incidence of clinically significant ECG abnormalities was similar among treatment groups (*Advair Diskus* 0, FP 1, salmeterol 0, and placebo 3 patients). Additionally, there were no observed treatment-related effects on vital signs or QTc.

5.4 Pivotal Efficacy and Safety Trials of *Advair Diskus* 250/50 on Reducing Exacerbations of COPD

Two replicate, randomized, double-blind, parallel-group studies compared the effect of *Advair Diskus* 250/50 with salmeterol 50 mcg each administered twice daily via the Diskus® device on the annual rate of moderate/severe exacerbations (primary endpoint) in patients with COPD.[46,47] Patients were at least 40 years of age, had an established clinical history of COPD (chronic bronchitis and/or emphysema) and no current diagnosis of asthma, had a pre-bronchodilator forced expiratory volume in one second (FEV_1) of 50% or less of predicted, an FEV_1/forced vital capacity (FVC) ratio of 70% of predicted or less, smoking history of at least 10 pack-years, and a documented history of one or more COPD exacerbations that required treatment with oral corticosteroids, antibiotics, or hospitalization during the last year before the

study. Following a 4 week run-in period, during which pharmacotherapy was optimized by treatment with open-label *Advair Diskus* 250/50 twice daily, patients were randomized in a double-blind fashion to *Advair Diskus* 250/50 or salmeterol 50 mcg twice daily.

The use of concurrent inhaled corticosteroids, inhaled long-acting bronchodilators (beta-agonist and anticholinergic), ipratropium and albuterol combination products, oral beta-agonists, leukotriene modifiers, and theophylline preparations were not allowed during the treatment period. Oral corticosteroids and antibiotics were allowed for the acute treatment of COPD exacerbations. Patients used albuterol on an as-needed basis throughout the study.

For identification of COPD exacerbations, patients recorded daily ratings of major symptoms of dyspnea, sputum volume, sputum purulence, and minor symptoms of sore throat, colds, fever, and wheeze or cough. A COPD exacerbation was defined as worsening of 2 or more major symptoms or worsening of 1 major symptom and 1 minor symptom for at least 2 consecutive days. COPD exacerbations that were self-managed by the patients and not associated with use of oral corticosteroids or antibiotics were defined as mild in severity. COPD exacerbations that required treatment with oral corticosteroids, antibiotics, or hospitalization were defined as moderate/severe.

Study 1 included 394 patients randomized to *Advair Diskus* and 388 patients randomized to salmeterol.[47] Similarly, Study 2 included 394 patients randomized to *Advair Diskus* and 403 patients randomized to salmeterol.[46] Patient demographics and baseline characteristics were similar between treatment groups in each study. In both studies the mean age was 65 years, and the mean FEV_1 was 33-34% of predicted.

The annual rate of moderate/severe COPD exacerbations was significantly lower by approximately 30% in the group treated with *Advair* compared with salmeterol in each study (Table 13). In each study the number of patients needed-to-treat to prevent one moderate/severe exacerbation per year was 2.[125]

Table 13. Annual Rate of Moderate/Severe COPD Exacerbations[46,126,47]

	Study 1 (SCO40043)		**Study 2 (SCO100250)**	
	***Advair Diskus* 250/50 (N=391)**	**Salmeterol 50 mcg (N=385)**	***Advair Diskus* 250/50 (N=385)**	**Salmeterol 50 mcg (N=393)**
Number of Patients with an Exacerbation, n (%)	211 (54)	230 (60)	208 (54)	234 (60)
Total Number of Exacerbations	368	432	352	440
Number of Patients by Number of Events, n (%)				
0 exacerbations	180 (46)	155 (40)	177 (46)	159 (40)
1 exacerbation	112 (29)	109 (28)	117 (30)	119 (30)
2 exacerbations	56 (14)	74 (19)	58 (15)	62 (16)
≥3 exacerbations	43 (11)	47 (12)	33 (9)	53 (13)
Mean Exacerbation Rate*	1.06	1.53	1.10	1.59
Treatment Ratio (95% CI)	0.695 (0.582, 0.830)		0.696 (0.583, 0.831)	
P-value	*P*<0.001		*P*<0.001	
*Negative Binomial Regression Model				

In order to determine the effect of the inhaled corticosteroid withdrawal that may have occurred due to the open-label *Advair* run-in, exacerbations that occurred during the first 4 weeks or 8 weeks of therapy of Study 1 were removed.[47] Results showed that patients receiving *Advair* compared with salmeterol had a 27.3% (*P*<0.001) reduction and 24.9% (*P*=0.005) reduction in the rate of moderate/severe exacerbations with removal of exacerbations occurring during the first 4 weeks and 8 weeks of therapy, respectively.

Results of the secondary endpoints were supportive of the primary endpoint (Table 14). In both studies patients receiving *Advair* had a significant reduction in risk of time to first moderate/severe exacerbation and a reduction in the rate of exacerbations requiring oral corticosteroids compared with salmeterol.

Additionally, statistically greater lung function (as measured by FEV_1) at Endpoint was observed with *Advair* compared with salmeterol in each study.(46,126,47)

Table 14. Results of the Secondary Endpoints

	Study 1 (SCO40043)		Study 2 (SCO100250)	
	***Advair Diskus* 250/50**	**Salmeterol 50 mcg**	***Advair Diskus* 250/50**	**Salmeterol 50 mcg**
Mean Rate of Exacerbations Requiring OCS	0.66	1.09	0.81	1.23
Treatment Ratio (95% CI)	0.603 (0.471, 0.772) *P*<0.001		0.657 (0.530, 0.814) *P*<0.001	
Hazard Ratio of Time to First Moderate/Severe Exacerbation (95% CI)	0.75 (0.620, 0.906) *P*=0.003		0.726 (0.602, 0.876) *P*<0.001	
Mean Change in FEV_1 at Endpoint, ml	-16	-59	-29	-105
LS Mean Difference	47 *P*=0.04		70 *P*=0.001	

CI=confidence interval; FEV_1=forced expiratory volume in one second; LS=least squares; OCS=oral corticosteroids

A retrospective analysis of the pooled data from the two studies was conducted to evaluate other COPD exacerbation outcomes.(125) Results of this analysis showed patients receiving *Advair Diskus* had a significant reduction (*P*<0.001) in the annual rate of moderate/severe exacerbations requiring antibiotics and a significant reduction (*P*=0.017) in the annual rate of moderate/severe exacerbations requiring hospitalization.

In both studies, the most commonly reported adverse events were nasopharyngitis and pharnygolaryngeal pain which occurred in a similar percentage of patients in each treatment group.(46,126) Pneumonia was reported in a higher percentage of patients receiving *Advair Diskus* (6% and 7% in Study 1 and 2, respectively) compared to salmeterol (2% each study).

5.5 Pivotal Efficacy and Safety Trials with Advair HFA in Adult and Adolescents with Asthma

Pivotal Clinical Trials in Patients 12 Years and Older

Advair HFA 45/21 versus Fluticasone Propionate 44 mcg and Salmeterol 21 mcg Alone

A 12-week, multicenter, randomized, double-blind, placebo controlled trial compared the efficacy and safety of salmeterol CFC 42 mcg and FP CFC 88 mcg to *Advair HFA* 88/42.(62) Study groups (N = 360) consisted of patients with mild to moderate asthma (mean FEV_1 = 67-68% of predicted) receiving $beta_2$-agonists (short- or long-acting) or inhaled corticosteroids (ICS). Patients treated with ICS were receiving either beclomethasone dipropionate (252-336 mcg/day), triamcinolone acetonide (600-800 mcg/day), flunisolide (1000 mcg/day), FP (176 mcg/day of MDI aerosol or 200 mcg/day of inhalation powder) or budesonide (400-600 mcg/day). Patients on $beta_2$-agonists prior to randomization were receiving either salmeterol or a short-acting $beta_2$-agonist as needed.

After the 2-week placebo run-in phase, patients were randomized to treatment with two inhalations of *Advair HFA* 44/21, FP CFC 44 mcg, salmeterol CFC 21 mcg, or placebo HFA each via a metered-dose inhaler (MDI) twice daily. All patients received albuterol as needed via MDI.

Primary efficacy measures included area under the 12-hour serial FEV_1 curve relative to day 1 baseline for *Advair HFA* 88/42 versus FP CFC 88 mcg and morning pre-dose FEV_1 at endpoint and the probability of remaining in the study over time (withdrawals due to worsening asthma) for *Advair HFA* 88/42 versus salmeterol CFC 42 mcg. Secondary efficacy measures included morning (AM) and evening (PM) peak expiratory flow (PEF), daily patient-rated diary symptom scores, albuterol use, and nighttime awakenings. The patients' perceptions of health through use of the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7 point scale where 1 = maximum impairment and 7 = none) were also evaluated.

On treatment day 1, there was a significant difference in the mean percent change from baseline in serial FEV_1 for *Advair HFA* 88/42 (24%) compared with FP CFC 88 mcg and placebo HFA (9% and 6%, respectively; $P < 0.001$), but not *Advair HFA* 88/42 compared with salmeterol CFC 42 mcg (21%) (Figure 5). At week 12, there was a significant difference in the mean percent change from baseline in serial FEV_1 for *Advair HFA* 88/42 (32%) compared with FP CFC 88 mcg, salmeterol CFC 42 mcg, and placebo HFA (21%, 22% and 8%, respectively; $P \leq 0.007$). Mean AUC of FEV_1 was significantly greater for *Advair HFA* 88/42 on day 1 and at week 12 when compared with FP CFC 88 mcg and placebo HFA ($P < 0.001$) and at week 12 for salmeterol CFC 42 mcg ($P = 0.006$).

In addition, patients receiving *Advair HFA* 88/42 had a 27% improvement from baseline in AM predose FEV_1 at endpoint compared with 18%, 12%, and 5% in patients treated with FP CFC 88 mcg, salmeterol CFC 42 mcg and placebo HFA, respectively ($P \leq 0.012$ *Advair HFA* versus all comparisons). Improvements in FEV_1 were seen with *Advair HFA* 88/42 regardless of baseline asthma therapy.

Significantly fewer patients receiving *Advair HFA* 88/42 (2%) were withdrawn due to worsening asthma compared with salmeterol CFC 42 mcg (25%; $P < 0.001$) and placebo HFA (28%; $P < 0.001$), but no significant difference existed when compared with FP CFC 88 mcg (8%). Patients receiving *Advair HFA* 88/42 had a significantly greater probability of remaining in the study without being withdrawn due to worsening asthma than patients receiving salmeterol CFC 42 mcg or placebo HFA ($P < 0.001$).

Significant improvements in AM and PM PEF were seen in patients receiving *Advair HFA* 88/42. At endpoint, the group treated with *Advair HFA* 88/42 had a mean change in AM PEF of 58 L/min compared with 1 L/min, 25 L/min, 27 L/min in the placebo HFA, salmeterol CFC 42 mcg, FP CFC 88 mcg groups, respectively ($P \leq 0.006$, *Advair HFA* 88/42 versus placebo, salmeterol, FP). Furthermore, the changes in PM PEF were 48 L/min, 20 L/min, 16 L/min and 3 L/min for the groups treated with *Advair HFA* 88/42, FP CFC 88mcg, salmeterol CFC 42 mcg, or placebo HFA, respectively ($P \leq 0.006$ *Advair HFA* versus all comparisons). Patients receiving *Advair HFA* 88/42 had clinically meaningful improvements in overall asthma specific quality of life as defined by a difference between groups of ≥ 0.5 points in change from baseline AQLQ scores (difference in AQLQ score of 1.14 [95% CI 0.85, 1.44]) compared to placebo. Other efficacy results are listed in Table 15.

Figure 5. Mean Change from Baseline in Serial FEV_1 on Day 1 and Week 12 of Treatment

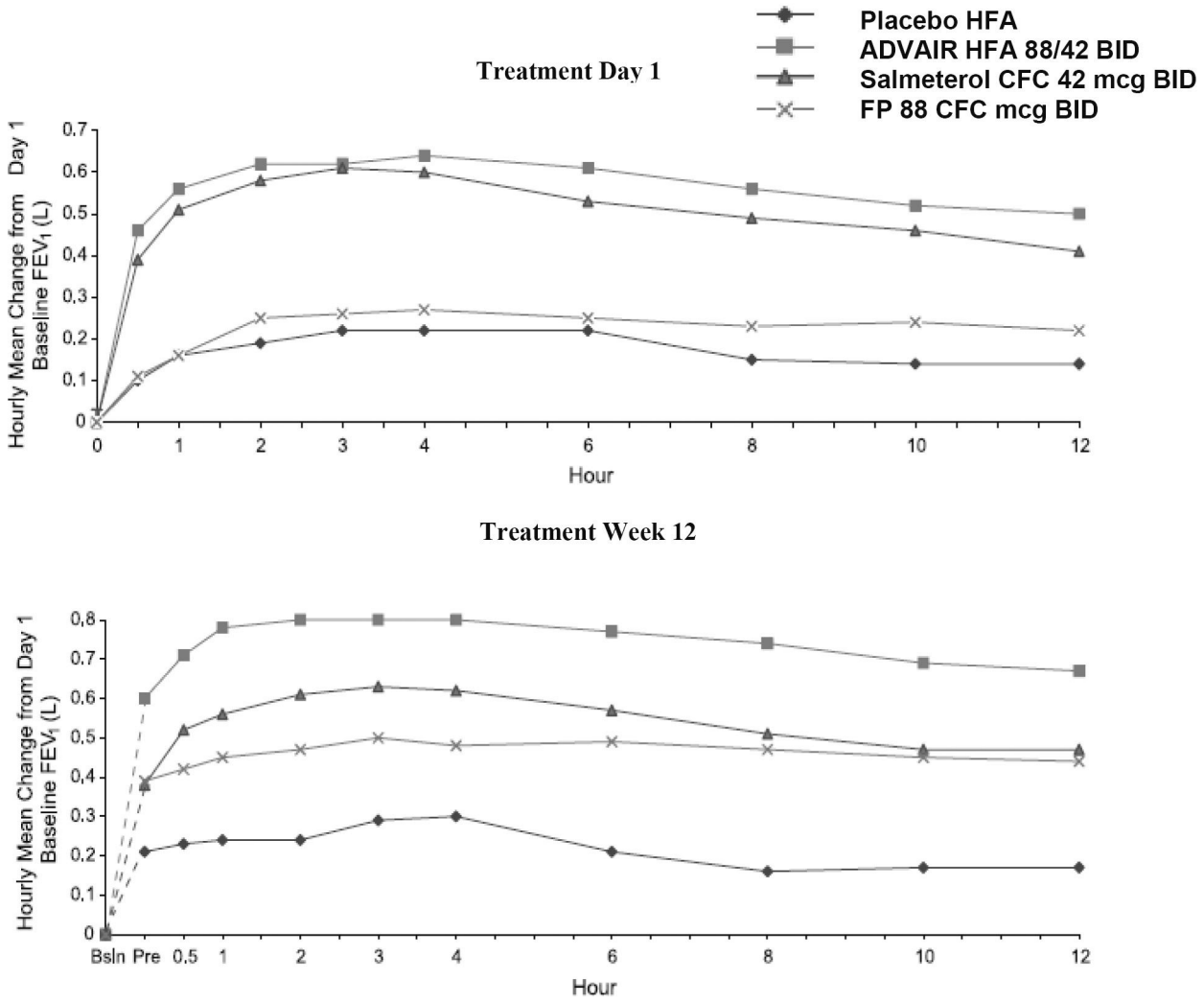


Table 15. Mean Change from Baseline at Endpoint in Secondary Efficacy Parameters[62]

	Advair HFA 88/42 mcg (n = 92)	FP CFC 88 mcg (n = 89)	Salmeterol CFC 42 mcg (n = 92)	Placebo HFA (n = 87)
Asthma Symptom Score				
Baseline	1.8	1.6	1.7	1.7
Mean change	-1.0*	-0.3	-0.4	0
% Of Days With No Asthma Symptoms				
Baseline	13	21.5	17.9	14.5
Mean change	39.7*	9.5	15.8	5.2
% Of Nights With No Awakenings				
Baseline	88.1	90.7	92.2	89.7
Mean change	9.0*	5.3	1.8	-4.3
% Rescue-free days				
*$P \leq 0.006$, *Advair HFA* vs. placebo, salmeterol, and FP				

	***Advair HFA* 88/42 mcg (n = 92)**	**FP CFC 88 mcg (n = 89)**	**Salmeterol CFC 42 mcg (n = 92)**	**Placebo HFA (n = 87)**
Baseline	25.7	38.4	28.4	29.3
Mean change	42.1*	13.5	21.1	3.2
*$P \leq 0.006$, *Advair HFA* vs. placebo, salmeterol, and FP				

All treatments had similar safety profiles and were well tolerated throughout the study. Drug-related adverse events were reported by 7%, 6%, 11% and 6% of patients treated with *Advair HFA* 88/42, FP CFC 88 mcg, salmeterol CFC 42 mcg, and placebo, respectively. The most commonly reported drug-related adverse events (≥ 2%) were throat irritation, hoarseness/dysphonia, headaches and cough.

A 12-week multicenter, randomized, double-blind, parallel-group comparison of *Advair HFA* 88/42 versus salmeterol CFC 42 mcg alone versus FP CFC 88 mcg alone was conducted in 283 adolescents and adults with moderate persistent asthma (mean FEV_1 = 65-67% of predicted) uncontrolled on as-needed short-acting $beta_2$-agonists alone. [64] During a 2-week run-in period, patients received albuterol as needed for relief of symptoms. At randomization, patients were assigned to one of three treatment groups: *Advair HFA* 44/21, FP CFC 44 mcg via MDI, or salmeterol CFC 21 mcg via MDI all administered as two inhalations twice daily. All patients received as-needed albuterol administered via MDI.

Primary efficacy measures included area under serial FEV_1 curve relative to day 1 baseline for 12-hour measurement of FEV_1 on treatment day 1 and treatment week 12 for *Advair HFA* 88/42 versus FP CFC 88 mcg and change from baseline at endpoint in morning pre-dose FEV_1 for *Advair HFA* 88/42 versus salmeterol CFC 42 mcg. Secondary efficacy measures included AM PEF, PM PEF, daily patient-rated diary symptom scores, albuterol use, nighttime awakenings and withdrawal due to worsening asthma.

On treatment day 1, there was a significant difference in the mean percent change from baseline in serial FEV_1 for *Advair HFA* 88/42 (25%) compared with FP CFC 88 mcg (9%, $P < 0.001$), but no significant difference between *Advair HFA* 88/42 and salmeterol CFC 42 mcg (26%). At week 12, there was a significant difference in the mean percent change from baseline in serial FEV_1 for *Advair HFA* 88/42 (40%) compared with FP CFC 88 mcg and salmeterol CFC 42 mcg (27% and 24%, respectively; $P \leq 0.004$). Mean AUC of FEV_1 was significantly greater for *Advair HFA* 88/42 on day 1 and at week 12 when compared with FP CFC 88 mcg ($P < 0.001$) and at week 12 for salmeterol CFC 42 mcg ($P = 0.013$).

In addition, patients receiving *Advair HFA* 88/42 had a 33% improvement from baseline in morning predose FEV_1 at endpoint compared with 25% and 22% improvement in patients treated with FP CFC 88 mcg or salmeterol CFC 42 mcg, respectively ($P \leq 0.048$ *Advair HFA* versus all comparisons).

Significantly fewer patients receiving *Advair HFA* 88/42 (1%) were withdrawn due to worsening asthma compared with salmeterol CFC 42 mcg (8%; $P = 0.024$), but no significant difference existed when compared with FP CFC 88 mcg (3%).

Significant improvements in AM and PM PEF were seen in patients receiving *Advair HFA* 88/42. At endpoint, the group treated with *Advair HFA* 88/42 had a mean change in AM PEF of 66.5 L/min compared with 43.0 L/min and 29.2 L/min in the FP CFC 88 mcg and salmeterol CFC 42 mcg groups, respectively ($P \leq 0.002$, *Advair HFA* 88/42 versus salmeterol and FP). Similar changes were noted for PM PEF. In addition, patients receiving *Advair HFA* had a mean change in percentage of rescue-free days of 40% compared with 26.5% in the FP group ($P \leq 0.028$). There were no significant differences in asthma symptoms scores, symptom-free days, nighttime awakenings, or albuterol use (puffs/day) between treatment groups.

All treatments were well tolerated throughout the study. Drug-related adverse events were reported by 17%, 16%, and 15% of patients treated with *Advair HFA* 88/42, FP CFC 88 mcg, and salmeterol CFC 42 mcg, respectively. The most commonly reported drug-related adverse events (≥ 2%) were throat irritation, hoarseness/dysphonia, headaches, candidiasis of the mouth or throat, and cough.

<u>*Advair HFA* 115/21 versus Fluticasone Propionate 110 mcg and Salmeterol 21 mcg Alone</u>

A 12-week, multicenter, randomized, double-blind, parallel group, placebo-controlled trial compared the efficacy of *Advair HFA* 220/42 , salmeterol CFC 42 mcg, and fluticasone propionate CFC 220 mcg.[127]

The study evaluated 365 adult and adolescent patients with mild to moderate persistent asthma (mean FEV_1 = 68-69% of predicted) previously treated with moderate doses of inhaled corticosteroids. Prior to randomization, patients were receiving treatment with beclomethasone dipropionate (378-840 mcg/day), triamcinolone acetonide (900-1600 mcg/day), flunisolide (1250-2000 mcg/day), FP (440-660 mcg/day of MDI aerosol or 400-600 mcg/day of inhalation powder) or budesonide (800-1200 mcg/day).

After a 2-week run-in period, use of inhaled corticosteroids was discontinued, and patients were randomized to treatment with either *Advair HFA* 110/21, salmeterol CFC 21 mcg, FP CFC 110 mcg, or placebo HFA each given as two inhalations twice daily. All patients received as needed albuterol via MDI.

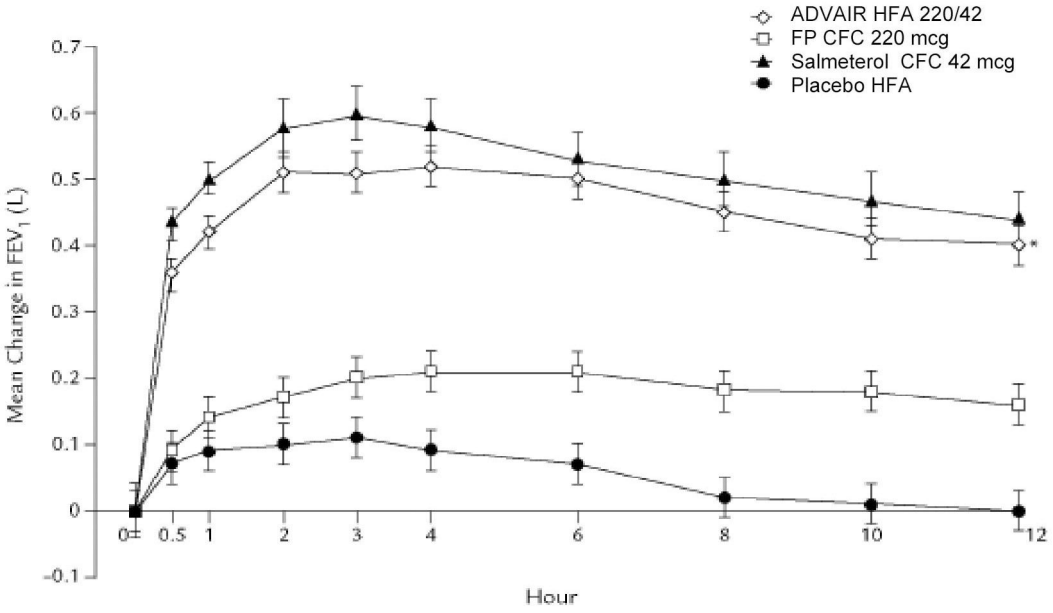
Primary efficacy measures included area under the 12-hour serial FEV_1 curve relative to day 1 baseline for *Advair HFA* 220/42 versus FP CFC 220 mcg and change from baseline in morning pre-dose FEV_1 at endpoint and the probability of remaining in the study over time (withdrawals due to worsening asthma) for *Advair HFA* 220/42 versus salmeterol CFC 42 mcg. Secondary efficacy measures included AM PEF, PM PEF, daily patient-rated diary symptom scores, albuterol use, and nighttime awakenings requiring rescue albuterol.

On treatment day 1, there was a significant difference in the mean percent change from baseline in serial FEV_1 for *Advair HFA* 220/42 (20%) compared with FP CFC 220 mcg and placebo HFA (6% and 0.06%, respectively; $P < 0.001$), but not compared with salmeterol CFC 42 mcg (22%) (Figure 6). At week 12, there was a significant difference in the mean percent change from baseline in serial FEV_1 for *Advair HFA* 220/42 (26%) compared with FP CFC 220 mcg, salmeterol CFC 42 mcg, and placebo HFA (11%, 19% and 4%, respectively; $P \leq 0.011$) (Figure 7). Mean FEV_1 AUC was significantly greater for *Advair HFA* 220/42 on day 1 when compared with FP CFC 220 mcg and placebo HFA ($P < 0.001$) and at week 12 for FP CFC 220 mcg, salmeterol CFC 42 mcg, and placebo HFA ($P \leq 0.02$). At endpoint, patients receiving *Advair HFA* 220/42 had a 20% improvement from baseline in morning predose FEV_1 compared with 9% and 8% improvement from baseline for FP CFC 220 mcg and salmeterol CFC 42 mcg, respectively, and -6% decline in patients receiving placebo HFA ($P \leq 0.001$ for all comparisons).

Significantly fewer patients receiving *Advair HFA* 220/42 (7%) were withdrawn due to worsening asthma compared with salmeterol CFC 42 mcg (24%; $P < 0.001$) and placebo HFA (54% $P < 0.001$), but no significant difference existed when compared with FP CFC 220 mcg (11%).

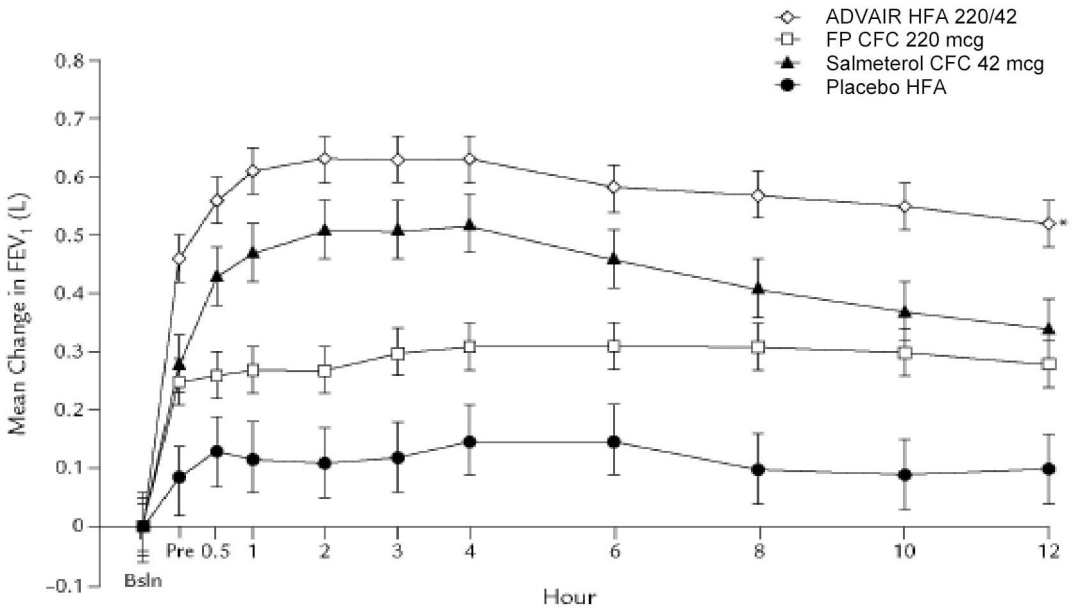
Improvements in secondary efficacy measures were also seen in patients treated with *Advair HFA* 220/42 (Table 16).

Figure 6. Mean Change from Baseline in Serial FEV_1 on Day 1 of Treatment



*P< 0.001 *Advair HFA* versus FP and placebo

Figure 7. Mean Change from Baseline in Serial FEV_1 at Week 12 of Treatment



*P< 0.02 *Advair HFA* versus FP, salmeterol, and placebo

Table 16. Mean Change From Baseline At Endpoint in Secondary Efficacy Parameters [127]

	Advair HFA 220/42 mcg (n = 94)	FP CFC 220 mcg (n = 91)	Salmeterol CFC 42 mcg (n = 91)	Placebo HFA (n = 89)
AM PEF (L/min)				
Baseline	342.6	344.4	344.3	347.4
Mean change	49.6*	13.9	13.2	-15.5
PM PEF (L/min)				
Baseline	368.9	368.4	367.3	371.5
Mean change	36.1*	9	5.4	-14.3
Asthma Symptom Score				
Baseline	1.6	1.6	1.7	1.5
Mean change	-0.5†	-0.2	-0.3	0.5
% of Days with No Asthma Symptoms				
Baseline	21.6	14.8	16.5	23.3
Mean change	18.5†	15	14	-9.1
% of Nights with No Awakenings				
Baseline	92.6	92.5	87.8	91.7
Mean change	4.1†	-0.6	-0.5	-14.8
Albuterol Use (puffs/day)				
Baseline	3.1	3.2	3.3	2.7
Mean Change	-1.6*	-0.5	-0.9	1.6
% of Rescue-Free Days				
Baseline	27.3	26.3	20.2	31.7
Mean change	32.5§	13.1	23.3	-13.9

*$P < 0.001$, *Advair HFA* vs. FP, salmeterol, and placebo

†$P < 0.001$, *Advair HFA* vs. placebo

§$P \leq 0.005$, *Advair HFA* vs. FP and placebo

All treatments were well tolerated throughout the study. Drug-related adverse events were reported by 10%, 14%, 5% and 4% of patients treated with *Advair HFA* 220/42, FP CFC 220 mcg, salmeterol CFC 42 mcg, and placebo HFA, respectively. The most commonly reported drug-related adverse events (≥ 2%) were headache, throat irritation, candidiasis of the mouth and throat, unspecified oropharyngeal plaques, and palpitations. There were no clinically significant changes from baseline in ECG changes, blood pressure, or heart rate. There were no differences between treatment groups in plasma or urinary cortisol concentrations.

Advair HFA 500/50 versus *Advair Diskus* 500/50 and Fluticasone Propionate 500 mcg

A 12-week, multicenter, randomized, double-blind, parallel-group comparison of *Advair HFA* 500/50 (dose of drug delivered from the canister valve) versus *Advair Diskus* 500/50 versus FP CFC 500 mcg alone was conducted in 509 adolescents and adults with moderate to severe asthma (mean FEV_1 = 71-74% of predicted) who were symptomatic on their current ICS therapy.[128] Prior to randomization, patients were receiving treatment with beclomethasone dipropionate (1500-2000 mcg/day), budesonide (1500-2000 mcg/day), flunisolide (1500-2000 mcg/day), or FP (750-1000 mcg/day).

After a 2-week run-in period, use of inhaled corticosteroids was discontinued, and patients were randomized to treatment with either *Advair HFA* 250/25 **two** inhalations twice daily, *Advair Diskus* 500/50 **one** inhalation twice daily, or FP CFC 250 mcg **two** inhalations twice daily. All patients received as needed albuterol. Baseline characteristics of the patients enrolled in this study are listed in Table 17.

Table 17. Mean Baseline Characteristics[128]

	Advair HFA 500/50 (n=176)	*Advair Diskus* 500/50 (n=161)	FP CFC 500 (n=172)
Age (years)	48	47	46
Male (%)	40%	40%	42%
Caucasian (%)	93%	92%	93%
Using a spacer (%)	20%	18%	17%
% Predicted FEV_1	73%	74%	74%

The primary efficacy measures was a change in mean morning PEF over weeks 1 to 12. To demonstrate equivalence between the *Advair HFA* and *Advair Diskus* groups, the 95% confidence intervals for the treatment difference in morning PEF had to fall within ± 15 L/min. Secondary efficacy measures included PM PEF, daytime and nighttime symptom scores, rescue albuterol use, and clinic FEV_1.

Over weeks 1 to 12, there was no significant difference in the mean change from baseline for AM PEF when comparing *Advair HFA* 500/50 with *Advair Diskus* 500/50 (Figure 8). The two *Advair* formulations were found to be equivalent based on the mean change in morning PEFR over weeks 1-12. In addition, no significant differences existed between *Advair HFA* and *Advair Diskus* for any of the secondary efficacy measures. When comparing *Advair HFA* with FP CFC, there was a significant difference in the primary endpoint of mean change from baseline in AM PEF ($P < 0.001$), evident after one week of treatment, as well as significant differences for all secondary endpoints ($P < 0.05$) over weeks 1 to 12. Primary and secondary efficacy results are summarized in Table 18. A comparison of *Advair Diskus* to FP CFC was not evaluated.

Figure 8. Mean Percent Change from Baseline in AM PEF in Patients Previously Treated With ICS

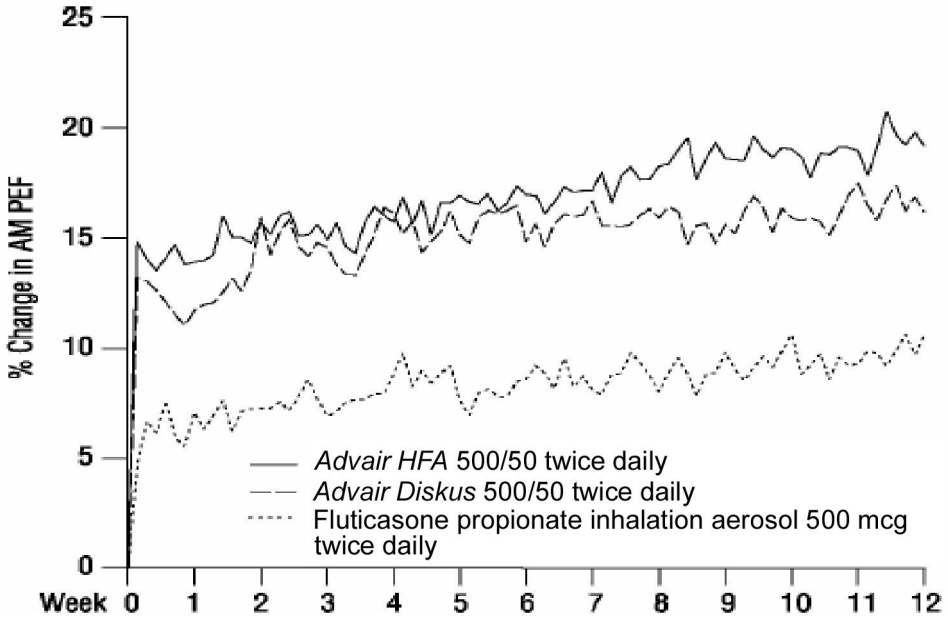


Table 18. Results of Primary and Secondary Outcomes [128]

	***Advair HFA* 500/50 (n = 176)**	***Advair Diskus* 500/50 (n = 161)**	**FP CFC 500 mcg (n = 172)**
Adjusted mean change in morning PEF (weeks 1-12)	50 L/min*	48 L/min	27 L/min
Adjusted mean change in evening PEF (weeks 1-12)	41 L/min*	38 L/min	21 L/min
Percentage of rescue-free days (weeks 1-12)	72%†	61%	45%
Percentage of rescue-free nights (weeks 1-12)	93%†	90%	79%
Percentage of symptom-free days (weeks 1-12)	38%†	26%	14%
Adjusted mean increase in FEV_1 (week 12)	0.27 L*	0.22 L	0.13 L
*$P < 0.001$ *Advair HFA* vs FP †$P < 0.05$ *Advair HFA* vs FP Comparison of *Advair Diskus* to FP was not evaluated.			

During the study, all treatments were well tolerated. Drug-related adverse events were reported in 13%, 11%, and 13% of patients in the *Advair HFA*, *Advair Diskus*, and FP CFC, respectively. The most commonly reported drug-related adverse event (≥ 2%) was hoarseness or dysphonia. Other drug-related adverse events had a low incidence (≤ 2%) and were similar among treatment groups. There was a significant difference in serum cortisol levels ($P = 0.014$) between *Advair HFA* and *Advair Diskus* at week 12, but not between *Advair HFA* and FP CFC. There were no significant differences in urinary cortisol excretion between the groups.

6. ADDITIONAL SAFETY INFORMATION

6.1 Studies Assessing the Effects of Salmeterol-Containing Products on Serious Asthma-Related Outcomes Including Exacerbations, Hospitalizations and Death in Patients with Asthma

Randomized Controlled Trials Evaluating Serious Asthma-Related Outcomes with Advair in Asthma

No specific studies have been conducted that have evaluated the effect of *Advair* on mortality in patients with asthma.

Randomized Controlled Trials Evaluating Serious Asthma-Related Outcomes with Salmeterol in Asthma

The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting $beta_2$-agonist–naive patients with asthma (average age of 39 years, 71% Caucasian, 18% African American, 8% Hispanic) to assess the safety of salmeterol inhalation aerosol 42 mcg twice daily over 28 weeks compared to placebo when added to usual asthma therapy. [69] [129]

The primary endpoint of this study was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). Secondary endpoints included combined asthma-related deaths or life-threatening experiences and asthma-related deaths. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355), which led to premature termination of the study. The results of the interim analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events. In

the total population, a higher rate of asthma-related death occurred in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%; relative risk 4.37 [95% CI 1.25, 15.34]).

Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). (129) In African Americans also, asthma-related death occurred at a higher rate in patients treated with salmeterol than those treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the relative risks of asthma-related death were similar in Caucasians and African Americans, the estimate of excess deaths in patients treated with salmeterol was greater in African Americans because there was a higher overall rate of asthma-related death in African American patients (Table 19).

Table 19. Asthma-Related Deaths in the 28-Week Salmeterol Multicenter Asthma Research Trial (129)

	Salmeterol N (%*)	**Placebo N (%*)**	**Relative Risk† (95% CI)**	**Excess Deaths Expressed per 10,000 Patients‡ (95% CI)**
Total Population§ Salmeterol: N = 13,176 Placebo: N=13,179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Salmeterol: N = 9,281 Placebo: N = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
African American Salmeterol: N = 2,366 Placebo: N = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

*Life table 28 week estimate, adjusted according to the patients' actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

†Relative risk is the ratio of the rate of asthma related death in the salmeterol group and the rate in the placebo group. The relative risk indicates how many more times likely an asthma related death occurred in the salmeterol group than in the placebo group in a 28 week treatment period.

‡Estimate of the number of additional asthma related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28 week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

§The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population includes those subjects whose ethnic origin was not reported. The results for Caucasian and African American subpopulations are shown above. No asthma related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma related death occurred in the placebo group in the subpopulation whose ethnic origin was not reported (salmeterol n = 130, placebo n = 127).

Baseline ICS Use

Inhaled corticosteroid use at baseline was reported by 47% of the overall population; 49% of Caucasians reported ICS use compared with 38% of African Americans. (69) For the overall population, the incidence of asthma-related deaths among patients who reported using ICS at baseline was similar regardless of treatment. However, there were more events in the salmeterol group compared with placebo, for those patients who reported no baseline ICS use (Table 20). Similar findings were seen in both Caucasian and African-American subgroups. Since SMART was not designed to evaluate the effects of ICS on study

outcomes, these data are not adequate to determine whether concurrent use of inhaled corticosteroids or other asthma controller therapy modifies the risk of asthma-related death.

Table 20. Incidence of Asthma-Related Deaths by Baseline Inhaled Corticosteroid Use, n (%) [69]

	Salmeterol (N=13,176)	**Placebo (N=13,179)**	**RR (95% CI)**
Overall Population			
Baseline ICS Use	4 (<1) (n=6127)	3 (<1) (n=6138)	1.3522 (0.3028, 6.0389)
No Baseline ICS Use	9 (<1) (n=7049)	0 (n=7041)	
Caucasian patients			
Baseline ICS Use	1 (<1) (n=4586)	1 (<1) (n=4637)	0.9604 (0.0601, 15.3502)
No Baseline ICS Use	5 (<1) (n=4695)	0 (n=4724)	
African-American patients			
Baseline ICS Use	3 (<1) (n=906)	1 (<1) (n=875)	3.1189 (0.3251, 29.9241)
No Baseline ICS Use	4 (<1) (n=1460)	0 (n=1444)	

Results in Pediatric Patients 12 to 18 Years of Age

A subgroup analysis of pediatric patients 12 to 18 years of age enrolled in the SMART study was conducted. A total of 1,653 pediatric patients were randomized to receive salmeterol 42 mcg twice daily, and 1,622 were randomized to the placebo group.[130] Baseline characteristics were similar between treatment groups. The majority of patients were male (51%-53%) with a mean age of 14.7-14.8 years and a mean FEV_1 of 89.1%-89.5% predicted. The treatment groups also were balanced with regard to ethnic origin. Pre-study asthma characteristics were similar across both treatments. The cohorts had a history of frequent emergency department (ED) visits for asthma (approximately 25% in the previous 12 months) and 6% of subjects in both groups had been hospitalized for asthma in the previous year. Nocturnal asthma symptoms affecting sleep occurred in approximately 50% of subjects.

Of the 3,275 subjects enrolled in the 12 to 18 year-old age group, 51 (2%) were hospitalized during the 28-week treatment period (Table 21). In this age group, 2 subjects in each treatment group experienced a primary outcome event; 1 of these events was a fatality (salmeterol group). Secondary outcome events were similar and the incidence did not exceed 2 events for either treatment, with the exception of all-cause hospitalization, experienced by significantly more subjects in the salmeterol group compared with the placebo group. The overall incidence of primary and secondary endpoints was similar between the patients 12 to 18 years of age and the adult patients.

Table 21. Overall Incidence of Primary and Secondary Endpoints in Pediatric Patients 12-18 Years of Age

Endpoint	12-18 Year-Olds (N=3,275)		≥19 Year-Olds (N=23,070)	
	Salmeterol 50 mcg BID	Placebo	Salmeterol 50 mcg BID	Placebo
n (%)	1,653 (50)	1,622 (50)	11,515 (50)	11,555 (50)
Primary Endpoint, n (%)				
Combined respiratory-related death or life-threatening experience	2 (<1)	2 (<1)	48 (<1)	34 (<1)
Secondary Endpoints, n (%)				
Respiratory-related death	1 (<1)	0	23 (<1)	11 (<1)
Combined asthma -related death or life-threatening experience*	2 (<1)	2 (<1)	35 (<1)	20 (<1)
Asthma-related death	1 (<1)	0	12 (<1)	3 (<1)
Combined all-cause death or life-threatening experience*	2 (<1)	2 (<1)	68 (<1)	57 (<1)
All-cause death	1 (<1)	0	41 (<1)	32 (<1)
All-cause hospitalization	35 (2)	16 (<1)	434 (4)	404 (3)
*Life threatening experience was defined as an event requiring intubation or mechanical ventilation.				

In addition, a post-hoc review of FDA MedWatch forms was performed to evaluate the relative risk of respiratory-related (including asthma) and asthma-related hospitalizations by treatment in the 12 to 18 year-old age group over the entire treatment period (Table 22). Of the 1,653 salmeterol-treated subjects in this age group, 18 (1%) were hospitalized due to a respiratory-related serious adverse events, 13 (<1%) of which were asthma-related. Of the 1,622 subjects in the placebo group, 9 (<1%) were hospitalized due to a respiratory-related serious adverse events, all of which were asthma-related. The comparison of asthma-related hospitalizations was not statistically significant between treatments. Regardless of reported ICS use at baseline, there was a higher number of respiratory-related hospitalizations with salmeterol compared with placebo (ICS use at baseline - salmeterol 10 vs. placebo 6; no ICS use at baseline - salmeterol 8 vs. placebo 3). There was no trend in any particular type of event within or across treatment groups for subjects 12 to 18 years of age who were hospitalized due to a non-respiratory-related event.

Table 22. Cumulative Relative Risk of Respiratory-Related Hospitalizations in Pediatric Patients 12-18 Years of Age

	Salmeterol 50 mcg BID	Placebo	Relative Risk (95% CI)
Subjects with All-Cause Hospitalization*	35 (2)	16 (<1)	2.0668 (1.1489, 3.7181)
Subjects with a Respiratory-Related Hospitalization (including asthma)	18 (1)	9 (<1)	1.8974 (0.8551, 4.2102)
Subjects with an Asthma-Related Hospitalization	13 (<1)	9 (<1)	1.3689 (0.5869, 3.1930)
Subjects with Other Respiratory-Related Hospitalization†	5 (<1)	0	N/A
Subjects with Non-Respiratory-Related Hospitalization	17 (1)	7 (<1)	2.2908 (0.9528, 5.5078)

CI = confidence interval

*All-cause hospitalizations included respiratory-related hospitalizations and non-respiratory-related hospitalizations which includes, but is not limited to, depression, appendicitis, miscarriage, dehydration, broken leg, auto accident, overdose of aspirin, and hydrocephaly.

†Other respiratory-related events include pneumonia, viral infection of the lung, and acute pharyngitis.

The *Serevent* Nationwide Surveillance (SNS) study was a 16-week study in over 25,000 patients with asthma comparing salmeterol to regular use of salbutamol (albuterol).[131] Patients were randomized 2:1 to receive salmeterol 50 mcg twice daily or albuterol 200 mcg four times daily. The results of SNS noted a higher, though non-significant, number of asthma-related deaths (12 vs. 2; *P*=0.105) in salmeterol recipients compared with regular use of albuterol (Table 23).

Table 23. Results of the SNS Study[131]

Outcome	Salmeterol (n=16,787)	Albuterol (n=8393)	Relative Risk *P*-Value
All Serious Events and Withdrawals	4272 (25.5%)	2209 (26.3%)	0.97 (*P* =0.200)
Asthma-related Deaths	12 (0.07%)	2 (0.02%)	3.0 (*P* =0.105)
Asthma-related Hospitalizations	193 (1.15%)	102 (1.22%)	0.95 (*P* =0.651)
Asthma-related Withdrawals	488 (2.91%)	318 (3.79%)	0.77 (*P* =0.0002)

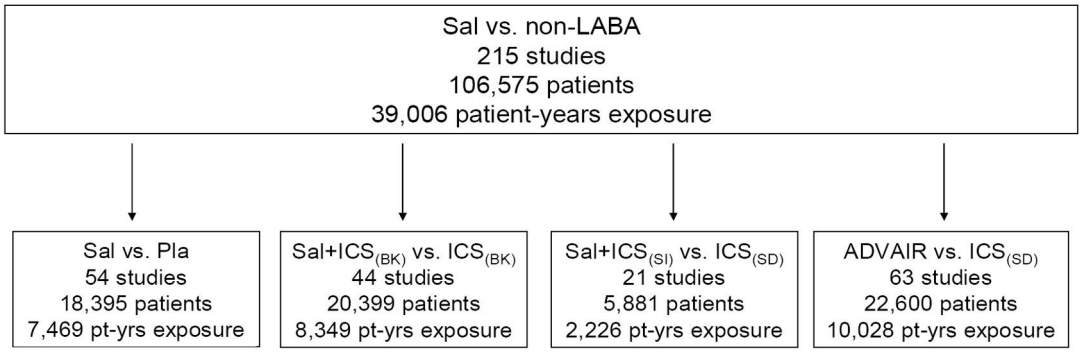
Meta-Analysis of GlaxoSmithKline (GSK) Studies Comparing Salmeterol Alone or in Combination with an ICS with Non-Long-Acting Beta$_2$-Agonist (LABA) Treatments

A meta-analysis of all randomized, double-blind, chronic dosing studies of salmeterol-containing products conducted by GlaxoSmithKline (GSK) evaluated the safety profile of salmeterol when used with an ICS both in a single inhaler and in separate inhalers, or when used without an ICS.[70] A total of 215 studies including 106,575 patients were included in the analysis. These totals include data from both Serevent Nationwide Surveillance Study (SNS) and SMART. The outcomes of interest were asthma-related death, asthma-related hospitalization, asthma-related intubation, and all-cause death.

Analysis populations were constructed for each of the five treatment comparisons of interest. For a study to be included in a specific analysis population, both treatment categories for comparison must have been present within the same study (Figure 9). This approach allows for control of important study differences such as different doses of ICS, changing standards of care, and different disease severity which could confound results. The salmeterol versus non-long-acting beta-agonist comparison (designated as Sal vs non-LABA; 215 studies, N=106,575) includes the largest number of studies and patients, but represents the most heterogeneous comparison since it includes salmeterol in any form (i.e., salmeterol alone or salmeterol plus ICS or *Advair*) compared with any non-LABA matched treatment study arm (i.e., ICS, leukotriene modifier, placebo, scheduled short-acting beta$_2$-agonist, etc.). The salmeterol versus placebo comparison (designated as Sal vs Pla; 54 studies, N=18,395) evaluates the safety of salmeterol in the absence of an ICS. In evaluating the use of salmeterol with an ICS, the ICS could be administered three different ways: 1) the addition of salmeterol to background ICS (ICS_{BK}) which refers to patients who

reported taking ICS prior to the study and were instructed to continue that ICS throughout the treatment period of the study (designated as Sal + ICS_{BK} vs ICS_{BK}; 44 studies, N=20,399); background ICS was not dispensed as part of the protocol nor was there systematic reinforcement or any measure of continued adherence to the medication 2) the addition of salmeterol to ICS administered as blinded study medication (ICS_{SD}) that was part of the study protocol administered in separate inhaler (SI) devices (designated as Sal + ICS_{SI} vs ICS_{SD}; 21 studies, N=5,881) 3) and salmeterol and ICS (fluticasone propionate) in a single device as *Advair* (designated as *Advair* vs ICS_{SD}; 63 studies, N=22,600). Only the *Advair* vs ICS_{SD} analysis population assures the concurrent use of ICS each time a patient was exposed to salmeterol. Therefore, this population was the primary population to inform on the safety profile of salmeterol in the presence of an ICS.

Figure 9. Diagram of Analysis Populations for Meta-Analysis



BK=background; SD=study drug; SI=separate inhalers

All serious adverse events were adjudicated from blinded case narratives by independent, external physicians. The primary measure for the analysis of the primary outcomes is the risk difference of rates between the treatment comparisons of interest.

A total of 35 asthma-related deaths were reported in the total population comparison of salmeterol versus non-LABA.[70] Of the 35 asthma-related deaths reported, 30 occurred in SMART and SNS together, accounting for 86% of the asthma-related deaths. Of the five asthma-related deaths not from SNS and SMART, three occurred in patients receiving salmeterol (two receiving salmeterol alone and one receiving salmeterol plus FP in separate inhalers) and two occurred in patients receiving other treatment (one receiving albuterol four times daily and one receiving placebo). There were no asthma-related deaths in the 11,437 patients who received *Advair*.

For studies where the concurrent use of salmeterol and ICS can be reasonably assured (e.g., *Advair* and Sal + ICS_{SI}), there was no evidence of increased risk for asthma-related death. However, when salmeterol was used in the absence of an ICS, an increase in asthma-related death were observed (Figure 10).

A total of 1,103 of the 106,575 patients in the analysis reported an asthma-related hospitalization (Figure 11). Overall, there was a statistically significant increase in the risk difference for asthma-related hospitalization for salmeterol compared with non-LABA and for Sal + ICS_{BK} compared with ICS_{BK}. The risk difference for asthma-related hospitalization was higher in patients who used salmeterol without an ICS and when ICS use was not controlled or dispensed by the protocol (i.e., salmeterol as blinded study drug added to background ICS). Risk difference decreased when patients used both salmeterol and ICS as dispensed study drugs. No increased risk was observed in patients who received *Advair* compared with an ICS.

Results for asthma-related intubations and all-cause death were consistent with the results for asthma-related death and hospitalizations (data not shown).

Figure 10. Meta-Analysis: Risk Difference for Asthma-Related Death (0.5 Continuity Correction)

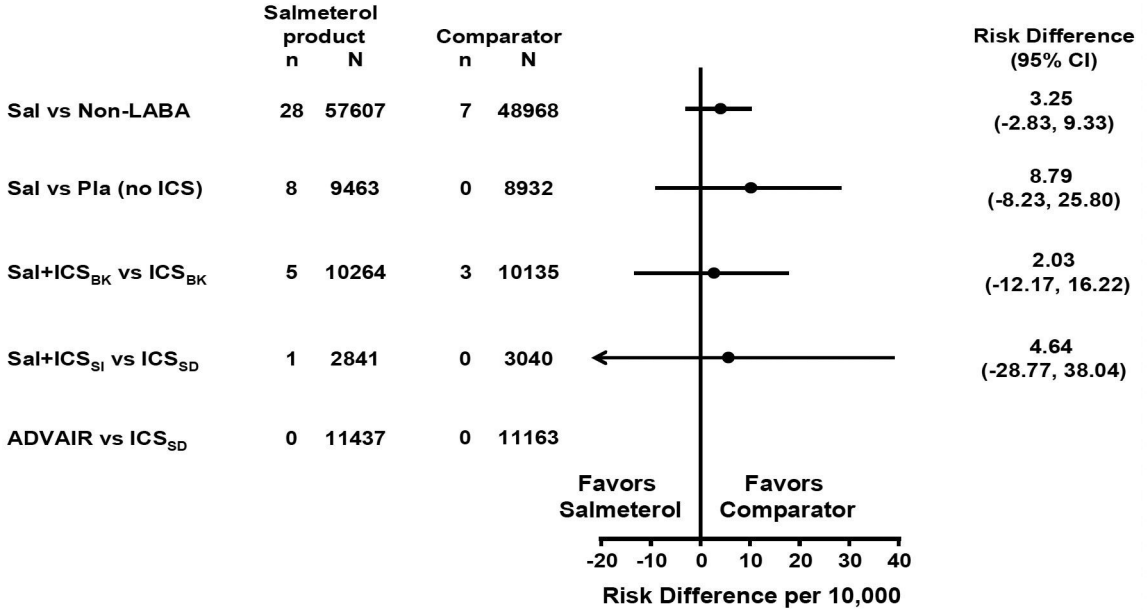
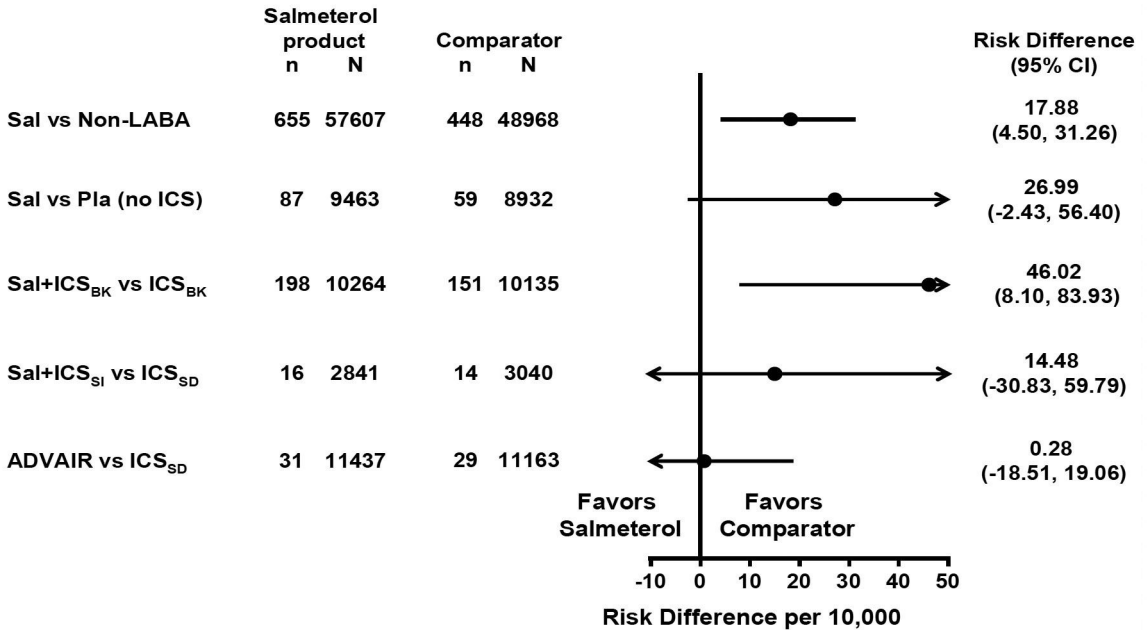


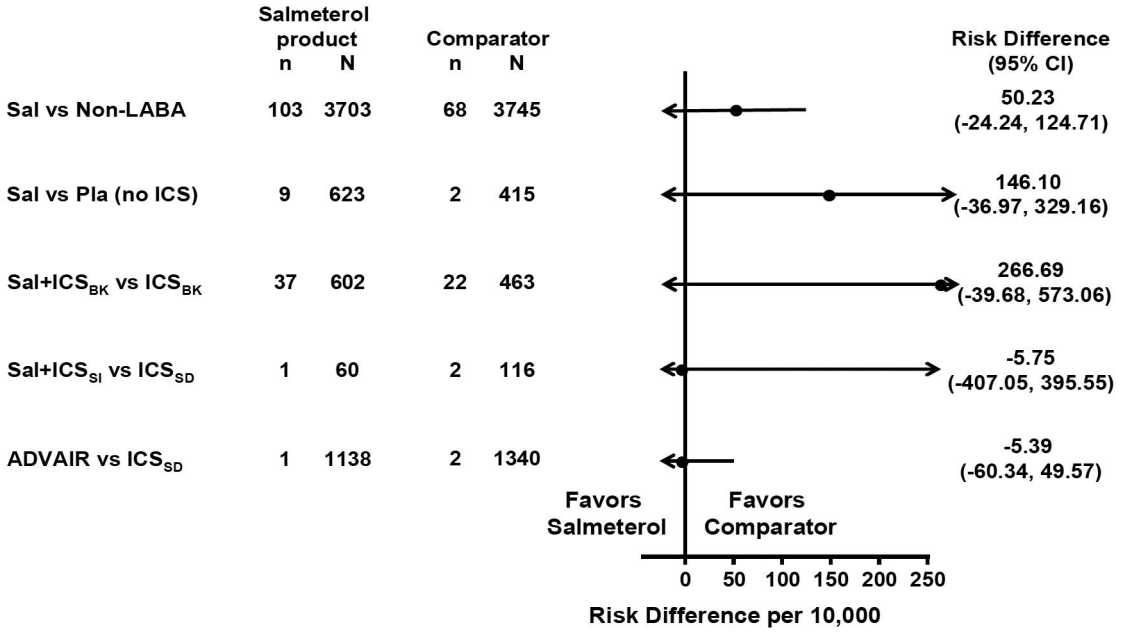
Figure 11. Meta-Analysis: Risk Difference for Asthma-Related Hospitalizations (0.5 Continuity Correction)



As part of this meta-analysis, an analysis of 37 studies which included pediatric patients less than 12 years of age was conducted.[70] Only one pediatric asthma-related death was reported in a patient was receiving albuterol four times daily. There was one intubation each for a patient receiving albuterol four times daily and in one receiving salmeterol without concurrent ICS.

Overall, the risk of asthma-related hospitalizations from studies in children were consistent with the total population and suggest patients taking salmeterol in the absence of ICS may be at increased risk of asthma-related hospitalizations (Figure 12). However, when salmeterol and ICS were used concurrently either as study drug (Sal + ICS_{SI}) or as *Advair*, there appeared to be no increased risk of asthma-related hospitalizations in children. Also, similar to the data in the overall population, the risk was elevated when salmeterol was administered with background ICS therapy (ICS_{BK}) compared with background therapy alone.

Figure 12. Meta-Analysis: Risk Difference for Asthma-Related Hospitalizations (0.5 Continuity Correction): Pediatric Population



Meta-Analysis of GSK Studies Comparing ICS Plus Salmeterol with ICS Alone

Asthma-Related Death or Hospitalization

A meta-analysis was performed on all clinical trials conducted by GSK comparing treatment with an ICS plus salmeterol with an ICS alone (higher or equal dose) in patients 4 years and older with asthma to assess the incidence of serious asthma-related events (death, intubation, hospitalization and severe exacerbations).[71] Studies included were 1-52 weeks in duration, randomized, double-blind, parallel design, evaluating twice daily dosing with currently approved regimens in the U.S. and were conducted between 1991 and 2007.

The analysis included 66 studies with 20,966 patients. Risk difference and Peto odds ratio (OR) were calculated for each study; however, only studies with at least one event could be used in the calculation of the odds ratios. Adjudication was performed by three physicians independently reviewing blinded, serious event case narratives and adjudicating the asthma relationship for each event.

One asthma-related death occurred in a patient receiving fluticasone propionate plus salmeterol in separate devices and one intubation occurred in a patient receiving beclomethasone dipropionate plus salmeterol in separate devices. There was no increased risk of hospitalizations with salmeterol added to ICS compared with an ICS alone (35 vs 34, respectively; risk difference 0.0002, 95% CI -0.0019, 0.0023; *P*=0.84). The odds ratio for asthma-related hospitalization was 1.07 (CI, 0.66, 1.73; *P* = 0.79). These incidence of hospitalization was similar between the ICS plus salmeterol group and ICS alone group regardless of trial duration, the ICS dose (similar to or higher than doses in the ICS alone group), or if the ICS plus salmeterol was given via a single or separate devices.

In a subgroup analysis of pediatric studies (n=6) in 1575 patients 4 to 17 years of age, one pediatric subject in each treatment group experienced an asthma-related hospitalization.

Asthma Exacerbations

A subanalysis of severe exacerbations, defined as those that required systemic corticosteroids, was performed on U.S. studies (n=24) which included 7,549 patients.[71] Treatment with salmeterol plus inhaled corticosteroids significantly reduced the risk of severe asthma exacerbations compared with an ICS alone (Table 24).

Table 24. Exacerbations Requiring Systemic Corticosteroids

	Number of Patients with an Exacerbation (%)	Patients	Risk Difference (95% CI)	Peto Odds Ratio (95% CI)
ICS + SAL (via single or separate devices)	175 (4.9)	3541	-0.025 (-0.036, -0.014) $P < 0.001$	0.65 (0.54, 0.79) $P < 0.001$
ICS	334 (8.3)	4008		
SAL+ FP (via single device)	67 (2.9)	2298	-0.012 (-0.023, -0.002) $P = 0.025$	0.71 (0.53, 0.96) $P = 0.026$
ICS	144 (5.6)	2556		
ICS + SAL (via separate devices)	108 (8.7)	1243	-0.048 (-0.071, -0.024) $P < 0.001$	0.61 (0.48, 0.78) $P < 0.001$
ICS	190 (13.1)	1452		

Other Published Meta-Analyses Comparing LABAs Alone or in Combination with an ICS with Non-LABA Treatments

Several randomized controlled trials and meta-analyses in patients of varying ages have evaluated the effect of LABAs with or without concurrent ICS on serious asthma-related outcomes including hospitalizations, life-threatening events, and death. [69,131,132,133,134] [135] [136] [137,138] In randomized, controlled trials and meta-analyses comparing LABA with placebo or albuterol, there was an increased risk of serious asthma-related events. [69,131,132,133] In meta-analyses conducted to determine the effect of adding a LABA to an ICS, there was no increased risk for asthma-related exacerbations, hospitalizations, and/or death compared with patients receiving ICS alone. [134] [135] [136] [137,138]

Observational Studies Evaluating Serious Asthma-Related Outcomes

Meta-Analysis of Observations Studies with *Advair* in Adults

In a meta-analysis of observational studies conducted by GSK, the effect of *Advair* on hospitalizations and emergency department (ED) visits was compared with ICS alone in adult patients with asthma.[70] Four observational studies, with asthma-related hospitalizations and ED visits as separate endpoints, met the *a priori* criteria for inclusion into the meta-analysis. These studies were all cohort design and contributed a total of 82,996 patients, with 58,983 patients receiving *Advair* and 24,013 patients receiving ICS alone. *Advair* was associated with a statistically significantly lower risk of having an asthma-related hospitalization (OR 0.85, 95% CI 0.74-0.97) and asthma-related ED visits (OR 0.84, 95% CI 0.76-0.94) compared to ICS monotherapy (Figure 13 and Figure 14).

Figure 13. Meta-Analysis: Odds Ratio for Asthma-Related Hospitalization (Adults)

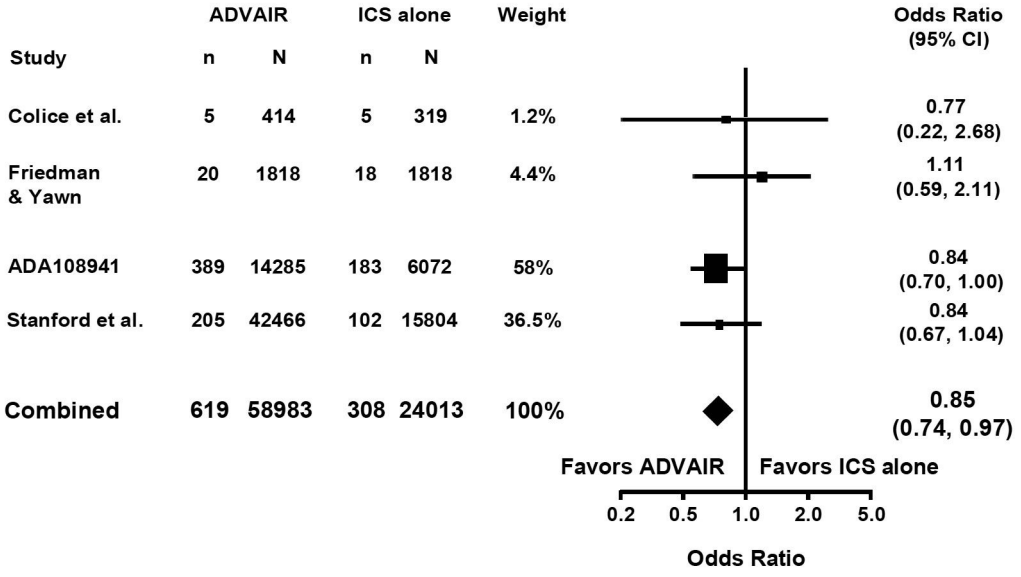
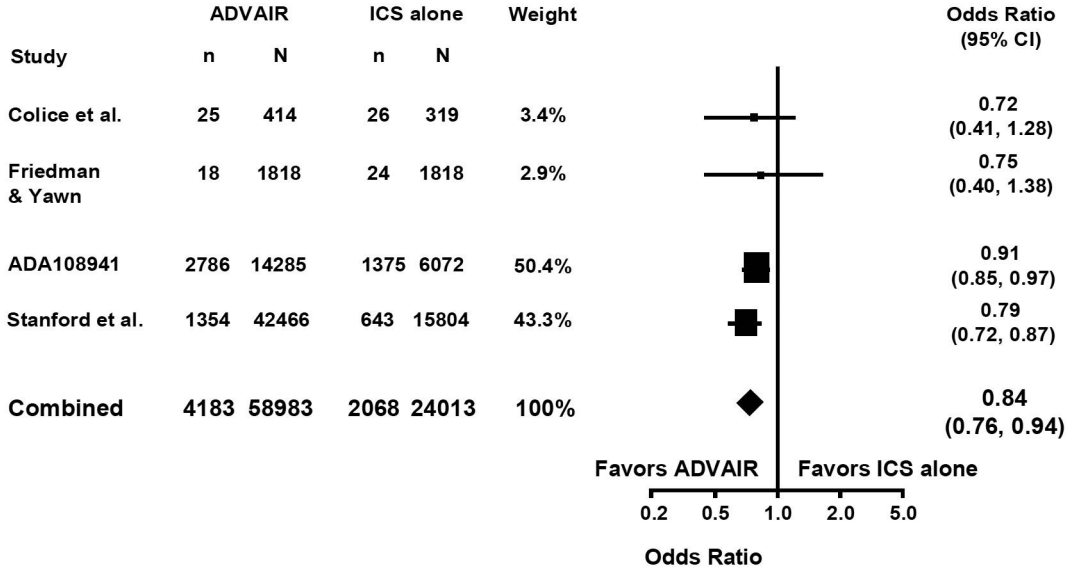


Figure 14. Meta-Analysis: Odds Ratio for Asthma-Related Emergency Department Visits (Adults)



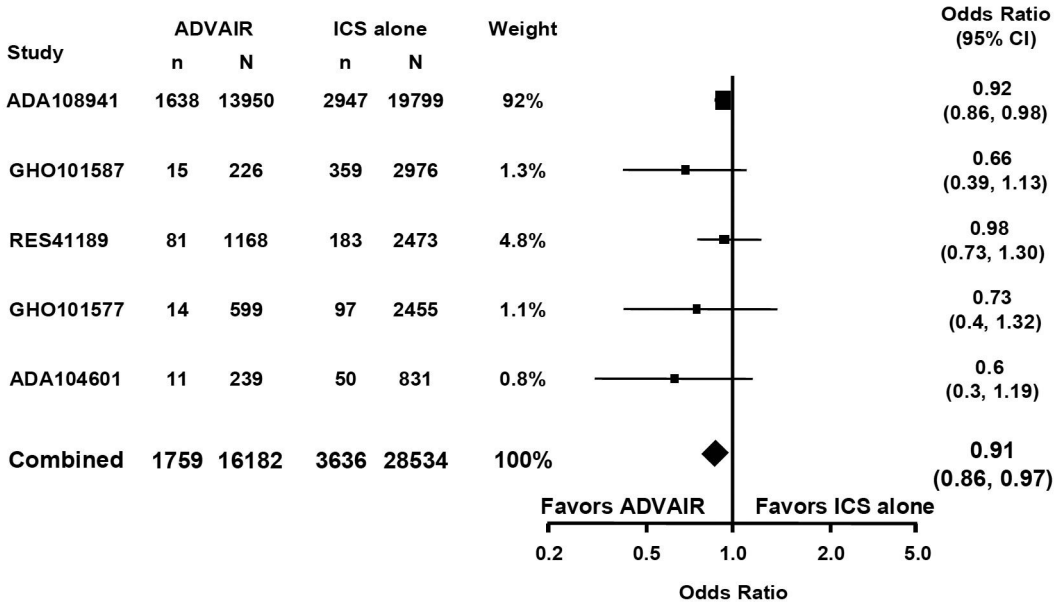
Meta-Analysis of Observational Studies with *Advair* in Children

In a meta-analysis of observational studies conducted by GSK, the effect of *Advair* on hospitalizations and emergency department (ED) visits was compared with ICS alone and ICS plus montelukast in pediatric patients with asthma.[70] Pediatric patients (N=46,500) were defined as 2 to 17 years of age. Due to the small number of hospitalizations observed in the studies, the combined endpoint of ED/hospitalization was reported for *Advair* compared with ICS and *Advair* compared with ICS plus montelukast.

Only one study (ADA108941) comparing *Advair* to ICS (fluticasone propionate) reported a separate adjusted risk ratio for asthma-related hospitalizations as an endpoint (hazard ratio 0.93; 95% CI 0.74, 1.16). Five studies met the *a priori* criteria for inclusion into the meta-analysis and reported these outcomes as a combined endpoint of ED visit/hospitalization, including a total of 44,716 patients with 16,182 receiving

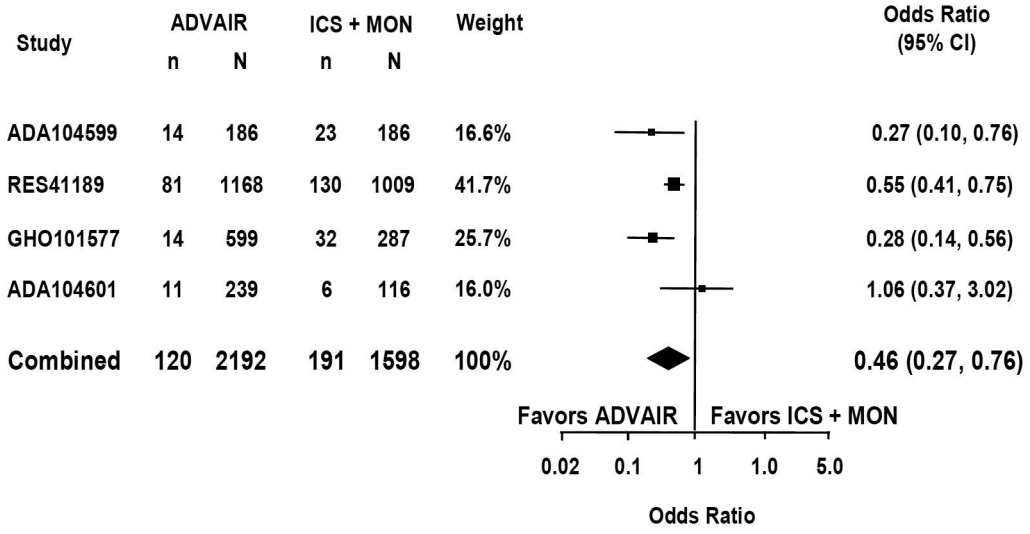
Advair and 28,534 receiving ICS. The analysis of these studies showed that *Advair* was associated with a statistically significantly lower risk of an asthma-related ED visit/hospitalization (OR 0.91, 95% CI 0.86-0.97) compared with ICS alone in pediatric patients (Figure 15).

Figure 15. Relative Risk for Asthma-Related Combined ED/Hospitalizations: ADVAIR vs. ICS, Pediatric Studies



Four studies met the *a priori* criteria and compared the risk of combined asthma-related ED visit/hospitalization endpoint for *Advair* with ICS plus montelukast, including a total of 3,790 pediatric patients with 2,192 receiving *Advair* and 1,598 receiving ICS plus montelukast. This comparison showed that *Advair* was associated with a statistically significantly lower risk of an asthma-related ED visit/hospitalization (OR 0.46, 95% CI 0.27-0.76) compared to ICS plus montelukast in pediatric patients (Figure 16).

Figure 16. Relative Risk for Asthma-Related Combined ED/Hospitalizations: ADVAIR vs. ICS Plus Montelukast, Pediatric Studies



Analysis of Exacerbations in a large study of African Americans

A randomized, double-blind, parallel group trial was designed to evaluate whether African American patients receiving *Advair Diskus* 100/50 have a lower rate of asthma-related exacerbations compared with African American patients receiving fluticasone propionate (FP) 100 mcg.[72] Patients included in the study were 12-65 years of age of African descent with persistent asthma who were symptomatic while receiving low-dose ICS (FP inhalation powder 250 mcg/day or equivalent). Patients were required to demonstrate a pre-albuterol forced expiratory volume in one second (FEV_1) between 60-90% of predicted after withholding asthma medications and have a documented history of reversibility (≥12%).

Patients who were symptomatic on their baseline ICS during a 2 week run-in period entered an open-label period were they received FP 250 mcg twice daily (BID). Patients next entered a 52-week double-blind treatment period and were assigned *Advair Diskus* 100/50 BID or FP 100 mcg BID. Patients who completed double-blind treatment entered a four week open-label FP 250 mcg BID run-out period. The primary efficacy endpoint was asthma exacerbation rate per patient per year. During the double-blind treatment period an asthma exacerbation was defined as worsening asthma that required treatment with an oral corticosteroid, hospitalization, or unscheduled urgent care (ie. physician office visit, emergency room visit) or a ≥30% decrease in FEV_1 from baseline, or morning peak expiratory flow below the established stability limit on two consecutive days. Secondary endpoints included morning peak expiratory flow, morning pre-dose FEV_1, percent symptom-free days, and percent albuterol-free days.

A total of 475 subjects were randomly assigned to treatment of which 239 received *Advair* and 236 received FP. Exacerbation rate was lower but not statistically significantly different in *Advair* compared with FP (Table 25).

Table 25. Mean Annual Asthma Exacerbation Rate Per Patient

	***Advair* 100/50** **n=239**	**FP 100 mcg** **n=236**
Exacerbation Rate	0.449	0.529
P-value	0.169	

The statistical plan for this study designated specific step-down rules for the testing of secondary efficacy measures. Since a significant treatment difference was not observed for the analysis of the primary efficacy measure, all comparisons for the secondary measures were declared not statistically significant. However, the statistical results are provided to help inform on the outcome of individual measures. Greater improvements were seen with *Advair* compared with FP for each of the secondary endpoints evaluated (Table 26).

Table 26. Secondary Efficacy Endpoints

	***Advair* 100/50**	**FP 100**	**LS Mean Difference (95% CI)**	***P*-Value**
AM PEF, L/min				
Baseline	342	340		
Mean Change	15.6	1.4	15.1 (5.5, 24.7)	0.002
AM Pre-dose FEV_1, L				
Baseline	2.53	2.52		
Mean Change	0.045	-0.061	0.103 (0.041, 0.165)	0.001
Symptom-free Days, %				
Baseline	26.7	23.2		
Mean Change	10.8	8.9	3.3 (-2.9, 9.6)	0.296
Albuterol-free Days, %				
Baseline	37.9	42.1		
Mean Change	10.8	5.6	4.5 (-1.8, 10.9)	0.159

Treatment with *Advair Diskus* 100/50 had a similar safety profile as FP 100 mcg. The overall incidence of non-serious adverse events were generally similar between the two treatment groups. The most common adverse events reported with *Advair* were headache and upper respiratory tract infection. The most common events reported with FP were headache, nasopharyngitis, upper respiratory infection, and sinusitis.

There were 25 serious adverse events reported among 20 patients. Eight patients receiving *Advair* and 12 patients receiving FP had a serious adverse event. Two patients treated with *Advair* and three patients treated with FP were hospitalized due to an asthma exacerbation. No deaths occurred during the study.

6.2 Studies Assessing Cardiovascular Safety of *Advair*

Clinical Studies in Patients with Asthma

Adults

Results of clinical efficacy studies with *Advair Diskus* and *Advair HFA* revealed that clinically significant ECG abnormalities occurred infrequently.[20,139,140,141] [142,143,144,145] There was no evidence that *Advair Diskus* or *Advair HFA* increased the incidence of QTc prolongation. Holter monitoring revealed no clinically significant dysrhythmias in patients receiving *Advair*. No patterns of clinically important treatment related changes in cardiac rate or rhythm were observed. The incidence of clinically significant ECG abnormalities was similar among patients treated with *Advair Diskus*, concurrent fluticasone propionate plus salmeterol therapy, salmeterol alone, fluticasone propionate alone, and placebo. During *Advair Diskus* clinical studies which monitored blood pressure and pulse rate, no treatment-related trends for changes in pulse rate or systolic/diastolic blood pressure were observed at any time.[18,20,139,140,141]

In a 1-year safety study of *Advair HFA*, clinically significant ECG changes were infrequent, and there was no significant change in mean heart rate determined by ECG with any strength of *Advair HFA*.[146]

Pediatrics

A 12-week safety study in 203 children with asthma aged 4 to 11 years compared *Advair Diskus* 100/50 with fluticasone propionate 100 mcg twice daily. [16,147] For all patients in both groups at 12 weeks, ECGs, mean heart rate, QTc intervals, and vital signs were considered normal or comparable to baseline values, as well as similar between groups.

The safety of *Advair HFA* 50/25 (ex-valve strength) two inhalations twice daily was compared to that of fluticasone propionate (FP) HFA inhalation aerosol 50 mcg (ex-valve strength) two inhalations twice daily in a multicenter, randomized, double-blind, double-dummy, parallel group study in 350 children with persistent asthma ages 4 to 11 years.[67]

At Treatment Week 12, mean heart rate and QTc intervals were similar between the treatment groups and comparable to baseline values. However, an unusually high frequency of ECG abnormalities were reported during the screening period as well as the post-randomization period. Adverse events related to ECG changes included prolonged QTc intervals (1% with *Advair HFA* and <1% with FP) and intraventricular conduction defects (2% in each group). When evaluating QTc intervals using the Fridericia correction formula, which has been suggested to be a preferred correction formula when evaluating patients with higher heart rates than adults (such as children), all patients with one exception had QTc (Fridericia) intervals less than the predefined abnormal threshold of 449 msec. Additionally, QRS durations in the *Advair HFA* group were within normal limits when corrected for age and gender. Furthermore, due to the unexpected high rate of reported ECG abnormalities at screening (prior to exposure to study treatment) and during the post-randomization period, an independent pediatric cardiologist, blinded to treatment and also to the central cardiologist's findings, performed a separate reading and interpretation of the ECGs in a subset of patients. This subset consisted of all patients who had a finding of "normal" ECGs at baseline and then "significant unfavorable change" post-randomization. This pediatric cardiologist confirmed that no clinically relevant ECG abnormalities were present in any patients in either the *Advair HFA* or the FP group.

Mean systolic and diastolic blood pressures were comparable between treatment groups at screening, and remained so throughout the study. Categorical increases or decreases from baseline in systolic or diastolic blood pressure were comparable in both treatment groups.

Clinical Studies in Patients with Chronic Obstructive Pulmonary Disease

Cardiac arrhythmias are common in patients with COPD with incidence varying between 20-86% in these patients.[148,149,150,151,152] Of note, there are several potential causes, including hypoxemia, hypercapnia, acid-base disturbance, cor pulmonale, methylxanthines, digitalis, and sympathomimetic agents,[152] including beta-agonists.[153] COPD patients are also at an increased risk for coronary artery

disease and heart disease due to chronic respiratory infection, a past history of smoking, and low high-density-lipoprotein cholesterol[154], which also increase the risk of arrhythmia.

The TORCH Study – Advair Diskus 500/50 Three-Year Study

The TORCH (TOwards a Revolution in COPD Health) study was a three-year, randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational study.[48] Patients with chronic obstructive pulmonary disease (COPD) (prebronchodilator forced expiratory volume in one second [FEV_1] <60% of predicted) were randomized to three-years of twice-daily treatment with either *Advair Diskus* 500/50, fluticasone propionate (FP) 500 mcg, salmeterol 50 mcg, or placebo. The primary endpoint was all-cause mortality.

In this study, 6184 patients were randomized to treatment; 6112 patients were included in the efficacy analysis (*Advair Diskus* n=1533, FP n=1534, salmeterol n=1521, placebo n=1524), and all 6184 patients were included in the safety analysis (*Advair Diskus* n = 1546, FP n = 1552, salmeterol n = 1542, placebo n = 1544). The mean age of the patients was 65 years, 76% were male, the mean post-bronchodilator FEV_1 was 44% of predicted, and 43% of the patients were current smokers.[48]

In the TORCH study, the incidence of cardiac adverse events was 17% in the *Advair Diskus* group, 21% in the placebo group, 20% in the fluticasone propionate group, and 19% in the salmeterol group.[155] [156]

The incidence of stroke events (cerebrovascular accidents and central nervous system hemorrhages) was 1.6% in the *Advair Diskus* group, 1.7% in the placebo group, 2.4% in the fluticasone propionate group, and 1.0% in the salmeterol group. Thus, there was no increase in cardiac or stroke adverse events with either *Advair Diskus* or salmeterol versus placebo.[156]

Patients were followed for up to 3 years to determine vital status. Cause of death was determined by a clinical endpoints committee. The incidence of cardiovascular deaths was 4% in the *Advair Diskus* group, 5% in the placebo group, 4% in the fluticasone propionate group, and 3% in the salmeterol group. A subset of cardiovascular deaths included deaths due to stroke or myocardial infarction. The incidence of deaths due to stroke was 0.5% in the *Advair Diskus* group, 0.4% in the placebo group, 1.0% in the fluticasone propionate group, and 0.3% in the salmeterol group. The incidence of deaths due to myocardial infarction was 0.6% in the *Advair Diskus* group, 0.7% in the placebo group, 0.3% in the fluticasone propionate group, and 0.2% in the salmeterol group. There was no evidence of increased risk of cardiovascular death, stroke or myocardial infarction in the *Advair* group compared with placebo.

12-Month Study with Advair Diskus 500/50

In a multicenter, randomized, parallel group, placebo-controlled trial comparing *Advair Diskus* 500/50 to the individual components at the same dose or placebo in over 1400 patients with COPD, ECG measurements (12-lead), heart rates (HR) and blood pressures (BP) were taken at baseline, weeks 24 and 52. At baseline, most (88-91%) of the patients in all treatment groups had normal or not clinically significant abnormal ECGs.[157]

Over the 52-week trial, the majority of patients in all treatment groups remained in the normal or not clinically significant abnormal range for their ECG. At week 52, negative changes from baseline ECG tracings (moving from normal/not clinically significant abnormal to abnormal/clinically significant) were noted in six patients in the *Advair Diskus* group, compared to 5 patients in the placebo group, 10 patients in the salmeterol group, and 6 patients in the FP group. In almost every case, these negative shifts were matched by patients with positive changes from baseline (from abnormal/clinically significant to normal/not clinically significant abnormal).

While not noted as clinically relevant, at week 52, mean HR changes from baseline ranged from -1.3 beats per minute (bpm) in the *Advair Diskus* group to +1.2 bpm in the placebo group. Also not noted as clinically relevant, at week 52, mean systolic BP changes from baseline ranged from –2.2 mmHg in the salmeterol group to +0.3 mmHg in the FP group and mean diastolic BP changes from baseline ranged from –1.0 mmHg in the salmeterol group to –0.2 mmHg in the FP group. Also not noted as clinically relevant, at week 52, mean systolic BP changes from baseline ranged from –2.2 mmHg in the salmeterol group to +0.3 mm Hg in the FP group and mean diastolic BP changes from baseline ranged from –1.0 mmHg in the salmeterol group to –0.2 mmHg in the FP group.

In this study, the incidence of cardiovascular adverse events was 10% in the *Advair Diskus* group, 9% in the placebo group, 9% in the fluticasone propionate group, and 11% in the salmeterol group.(158) The incidence of cardiovascular deaths was very low in each treatment group (*Advair* 0.6 %, placebo 1.1%, FP 0.8% and salmeterol 0.8%). Thus, there was no increase in cardiovascular adverse events or deaths with either *Advair Diskus* or salmeterol versus placebo.

Six-Month Studies with Advair Diskus 250/50 or 500/50

During two large pivotal clinical trials in patients with COPD, cardiovascular safety of *Advair Diskus* 500/50 and 250/50, each compared to the individual components and placebo, was monitored. These were randomized, double-blind, placebo-controlled, parallel group trials conducted over 24-weeks. A 12-lead electrocardiogram (ECG) was performed for each subject at screening, pre-dose at weeks 12 and 24, and/or at subject discontinuation visit. Subjects with clinically significant abnormal ECG's at screening were excluded. In addition, some of the subjects in the trial receiving *Advair Diskus* 500/50, fluticasone propionate (FP) 500 mcg, salmeterol 50 mcg and placebo were monitored via Holter monitoring at some point during the single-blind run-in, and at week 4. Monitoring started one hour prior to dose and continued for 24-hours. Patients with clinically significant abnormal findings on Holter tracings during run-in were not randomized into the trial. Lastly, vital signs were also monitored at select sites at baseline and again at week 12. On those dates, vital signs were recorded at times 0.5, 1, 2, 4, 6, 8, 10 and 12 hours post-dose.(159) (45)

Results from these clinical trials revealed that few subjects had clinically significant abnormal ECG findings. Overall incidences of significantly abnormal ECG results were lower in the salmeterol +/- fluticasone propionate treatment groups when compared to placebo (1% versus 3%, respectively). There was no evidence that co-administration of fluticasone propionate with salmeterol increased the incidence of QTc prolongation. In those who experienced a change from baseline, more changes were noted in older (≥65 years old) males compared to younger and/or female patients, but this effect was not noted to be treatment related. Holter monitoring revealed no significant differences of ventricular and supraventricular ectopic events and cardiac rates between treatment groups. No cases of sustained ventricular tachycardia were observed. No treatment effect was observed on pulse rate or systolic and diastolic blood pressure between treatment groups.(159) (160)

Other Studies With Advair Diskus 250/50

Clinical trials of *Advair Diskus* 250/50 in COPD were inadequate to evaluate the comparative incidence or risk of cardiac adverse events. (161,45,47,162) These trials were either of too short duration, enrolled too few patients, or did not have an placebo group.

6.3 Studies Assessing Risk of Pneumonia with *Advair* in COPD

Background: Association of Pneumonia and COPD

Regardless of treatment, patients with COPD may be at increased risk for developing pneumonia(163,164) and being hospitalized for pneumonia.(165,166,167,168) However, it is unclear whether patients with COPD who are hospitalized with pneumonia are at increased risk of death.(165,169)

Data regarding the occurrence of pneumonia with *Advair* in patients with COPD are available from randomized, double-blind, controlled, clinical trials of 1 to 3 years in duration. In these clinical trials, an adverse event was defined as any untoward, unfavorable, or unintended sign, symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug. In two studies, pneumonia diagnosis required confirmation by chest X-ray.(170,46) In all other studies, no specific diagnostic criteria were provided to the investigators.

<u>*Advair Diskus 250/50* Clinical Studies</u>

The rate of pneumonia adverse events during treatment with *Advair Diskus 250/50* in patients with COPD was calculated from a pooled analysis of two replicate, randomized, double-blind, parallel-group studies (SCO40043, SCO100250).(170,46,171) The primary endpoint of these studies was the rate of moderate/severe COPD exacerbations with *Advair Diskus* compared with salmeterol. During a 4-week run-in, patients received open-label *Advair Diskus 250/50* twice daily. Patients were then randomized to *Advair Diskus 250/50* or salmeterol 50 mcg twice daily for 1 year. Patients were ≥ 40 years of age with a diagnosis of

COPD and had a forced expiratory volume in one second (FEV_1) of ≤ 50% predicted, an FEV_1/forced vital capacity (FVC) ≤ 0.7, and a history of ≥ 1 exacerbation in the past year. Investigators were instructed to confirm the diagnosis of pneumonia by chest X-ray. The results are summarized in Table 27.

Table 27. Pneumonia Rate During Treatment with *Advair Diskus* 250/50[171]

	Advair Diskus 250/50 **(n=788)**	**Salmeterol (n=791)**
Number of patients with pneumonia (%)	55 (7%)	25 (3%)
Number of cases of pneumonia	56	27
Total exposure (years)	652	590
Rate per 1000 treatment-years	86	46

From this pooled analysis, it was determined that the number needed to harm (NNH) to have 1 additional patient with a pneumonia adverse event per year was 25.[125]

The TORCH Study: *Advair Diskus 500/50*

The TORCH study was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational study in patients with COPD.[48] Patients were randomized to twice-daily treatment with either *Advair Diskus 500/50* (n=1546), fluticasone propionate (FP) 500 mcg (n=1552), salmeterol 50 mcg (n=1542), or placebo (n=1544). The primary endpoint was all-cause mortality. The mean age of the patients was 65 years, 76% were male, the mean post-bronchodilator FEV_1 was 44% of predicted, and 43% of the patients were current smokers. The incidence of pneumonia was 13.4% with *Advair Diskus*, 11.9% with FP, 8.6% with salmeterol, and 7.3% with placebo.

Rate of Pneumonia Per Treatment Year

In the SCO40043, SCO100250 and TORCH studies, there was an uneven exposure to study drugs based on different proportions of patients withdrawing from each treatment arm.[46,48,126] The proportion of patients who withdrew from the SCO40043 and SCO100250 studies was higher in the salmeterol group (39%) than in the group receiving *Advair Diskus* (31%), resulting in an uneven exposure to the study drugs: *Advair Diskus* mean 303 days; salmeterol mean 274 days. The proportion of patients who withdrew from the TORCH study was higher in the placebo group (44.2%) than in the other three groups (*Advair Diskus* group 34.1%, FP group 38.3%, salmeterol group 36.9%), resulting in an uneven exposure to the study drugs: *Advair Diskus* 3700 treatment years; placebo 3278 treatment years; FP 3555 treatment years; and salmeterol 3531 treatment years. In addition to uneven exposure to study drugs, these studies were of different durations (1 year vs. 3 years, respectively) and used different doses of *Advair Diskus* (250/50 vs. 500/50, respectively).

Therefore, the rates of pneumonia (including all pneumonia-related events) were adjusted for time on treatment, as shown in Table 28. The rate of pneumonia does not appear to be dose-related, and one year or three year study duration does not appear to change the rate.

Table 28. Rate of Pneumonia* Per 1000 Treatment-Years

	Advair Diskus	**FP**	**Salmeterol**	**Placebo**
Pooled data from SCO40043[171] and SCO100250[46] *Advair Diskus 250/50* 1 year	86	—	46	—
TORCH[172] *Advair Diskus 500/50* 3 years	88	84	52	52
FP=fluticasone propionate *includes pneumonia and pneumonia-related terms				

Risk of Pneumonia in the Geriatric Population

In both TORCH and the exacerbation studies, the excess risk of pneumonia was higher in patients >65 years of age compared with patients <65 years of age (Table 29).[126,172,161]

Table 29. Occurrence of Pneumonia with *Advair Diskus* By Age

	TORCH (3-year study)		Exacerbation Studies (1-year studies)	
Percent of Patients with Pneumonia	**Placebo**	***Advair Diskus 500/50***	**Salmeterol**	***Advair Diskus 250/50***
Total Population	9%	16%	3%	7%
Patients <65 Years	8%	14%	3%	4%
Patients >65 Years	10%	18%	3%	9%

Pneumonia-related Serious Adverse Events and Death

Pooled results of the exacerbation studies show pneumonia-related serious adverse events were reported in 4% and 2% of patients treated with *Advair Diskus 250/50* and salmeterol, respectively.[46,126] Deaths due to pneumonia were reported 1 patient randomized to *Advair,* and none in the salmeterol group.

In the TORCH study, pneumonia-related serious adverse events were reported in 10% of patients in both the *Advair Diskus* and FP groups and in 6% of patients in both the placebo and salmeterol groups.[48] There was no increase in fatal events of pneumonia in the patients treated with *Advair Diskus*. Among patients receiving study medications, there were 8 deaths from pneumonia in the *Advair Diskus* group, 7 in the placebo group, 9 in the salmeterol group, and 13 in the FP group.

Meta-analysis of Occurrence of Pneumonia in Patients with COPD Treated with Advair

GlaxoSmithKline conducted a meta-analysis of randomized, double-blind clinical trials with *Advair* to assess reports of selected adverse events including pneumonia.[173] Studies were of at least 12 weeks duration with a steroid containing treatment arm (*Advair* or FP) and a non-steroid treatment arm in adults with COPD. Twelve studies with *Advair* enrolling 13,900 patients met the criteria. In 10 of the studies, the dose of *Advair Diskus* was 500/50 twice daily and in 2 studies, the dose was 250/50 twice daily. Of the 13,900 patients, 4679 (34%) were exposed to *Advair*. Among the patients treated with *Advair*, 54% were ≥65 years, 76% were male, and 60% had baseline post bronchodilator FEV_1 <50% of predicted. The mean duration of treatment with *Advair* was 48.4 weeks (range 12 to 156 weeks).

At least one pneumonia adverse event was reported by 8% of patients treated with *Advair* compared with 4% of patients receiving the main comparator (placebo, salmeterol or tiotropium). When adjusted for duration of exposure, the rate of pneumonia was 77 per 1000 treatment-years with *Advair* compared with 40 per 1000 patient-years with the comparator arm (salmeterol, tiotropium or placebo).

Mechanism of Pneumonia in Patients with COPD Receiving Advair

The biologic mechanism for a higher risk of pneumonia in patients receiving *Advair* is unclear. In the TORCH study, culture samples were not required for an investigator to make a diagnosis of pneumonia. However, 12% of serious adverse event reports of pneumonia mentioned that a culture sample was taken.[172] There was no evidence of opportunistic infections where cultures were obtained, and the nature of infection was compatible with those expected in a normal COPD population. Further, patients without culture-confirmed, non-fatal pneumonias responded to conventional antibiotics, which suggested that the pneumonias were not atypical or opportunistic. This trial could not ascertain whether any specific pathogen (e.g., bacterial, viral, or opportunistic) was causally associated with most of these reports.

6.4 Studies Assessing Effect on Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression with Advair

Clinical Studies with Advair Diskus in Asthma

Adult and Adolescent Patients with Asthma

***Advair Diskus* 100/50**

In a repeat-dose 3-way crossover study, 1 inhalation twice daily of *Advair Diskus* 100/50, fluticasone propionate (FP) 100 mcg via Diskus®, or placebo was administered to 20 adolescent and adult subjects

with asthma.[174] After 28 days of treatment, geometric mean serum cortisol area under the curve (AUC) over 12 hours showed no significant difference between *Advair Diskus* and fluticasone propionate, or between each active treatment and placebo.

Bateman, et al [17] conducted a 12-week, randomized, double-blind, double-dummy, parallel-group study comparing *Advair Diskus* 100/50 and concurrent use of FP 100 mcg twice daily plus salmeterol 50 mcg twice daily via separate *Diskus* devices in 244 patients with asthma (mean FEV_1=75-76% of predicted). Morning serum cortisol measurements were obtained at baseline and after 12 weeks of treatment. The geometric mean morning serum cortisol concentrations were similar between treatment groups at baseline and after 12 weeks. No differences in the frequency of serum cortisol abnormalities between the *Advair Diskus* and FP plus salmeterol groups were noted (11% versus 12%). In addition, there were fewer patients with abnormalities after treatment than at baseline (16% in the *Advair Diskus* group versus 20% in the FP plus salmeterol group).

***Advair Diskus* 250/50**

Shapiro, et al [8] conducted a 12-week, randomized, double-blind, parallel-group study comparing *Advair Diskus* 250/50, salmeterol 50 mcg twice daily via *Diskus*, FP 250 mcg twice daily via *Diskus*, and placebo in 349 patients (mean forced expiratory volume in one second [FEV_1]=66-69% of predicted). Morning plasma cortisol concentrations and response to ACTH stimulation at baseline and after 12 weeks of treatment were used to assess HPA axis effects. A normal plasma cortisol concentration was defined as ≥5 mcg/dl. A normal response to ACTH stimulation was defined as a plasma cortisol concentration of at least 18 mcg/dl and an increase from baseline of at least 7 mcg/dl.

No clinically significant differences in morning plasma cortisol or response to ACTH stimulation were observed among treatment groups. The table below illustrates the number of patients in the *Advair Diskus* group with abnormalities in morning plasma cortisol and responses to ACTH stimulation testing at baseline and after twelve weeks of treatment (Table 30).

Table 30. Abnormalities in morning plasma cortisol concentrations and ACTH stimulation [8]

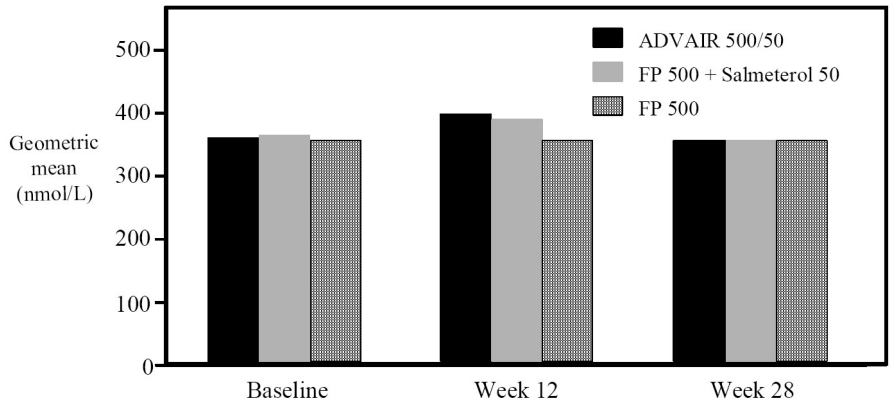
	***Advair Diskus* 250/50**	**FP 250 mcg**	**Salmeterol 50 mcg**	**Placebo**
No. (%) of patients with abnormal morning cortisol at baseline	0	1 (3%)	1 (3%)	1 (3%)
No. (%) of patients with abnormal morning cortisol after 12 weeks	1 (3%)	2 (6%)	0	2 (6%)
No. (%) of patients with post-stimulation change <7 mcg/dL at baseline	0	2 (6%)	4 (11%)	2 (5%)
No. (%) of patients with post-stimulation change <7 mcg/dL after 12 weeks	4 (11%)	3 (9%)	5 (15%)	3 (8%)
No. (%) of patients with post-stimulation cortisol <18 mcg/dL at baseline	0	1 (3%)	0	1 (3%)
No. (%) of patients with post-stimulation cortisol <18 mcg/dL after 12 weeks	1 (3%)	2 (6%)	0	2 (6%)
FP = fluticasone propionate				

***Advair Diskus* 500/50**

Aubier, et al [9] conducted a randomized, double-blind, double-dummy, parallel-group study comparing *Advair Diskus* 500/50, concurrent use of salmeterol 50 mcg twice daily plus FP 500 mcg twice daily via separate *Diskus* devices, and FP 500 mcg via *Diskus*. Treatments were administered for 28 weeks. A total of 503 patients (mean FEV_1=73% of predicted) participated in the study. Morning serum cortisol measurements were obtained at baseline and after 12 and 28 weeks of therapy. In addition, 24-hour urinary cortisol excretion corrected for creatinine were obtained in a subset of patients (n=318). There were no

significant differences in the change in serum cortisol levels or 24-hour urinary cortisol between the three treatment groups (Figure 17). Furthermore, there were no significant differences between baseline and 28-week measurements for these parameters for any of the treatment groups. The percentage of patients with an abnormal morning plasma cortisol concentration in the *Advair Diskus*, salmeterol plus FP, and FP groups was similar at baseline (9% versus 8% versus 9%), after 12 weeks (4% versus 6% versus 10%), and after 28 weeks (5% versus 11% versus 9%).

Figure 17. Serum Cortisol After 28 Weeks of Treatment



Pediatric Patients with Asthma

In a 12 week study in children aged 4 to 11 years with asthma who were receiving inhaled corticosteroids at study entry, *Advair Diskus* 100/50 twice daily was compared with FP 100 mcg twice daily via *Diskus*. The values for 24 hour urinary cortisol excretion at study entry and after 12 weeks of treatment were similar within each treatment group. After 12 weeks, 24 hour urinary cortisol excretion was also similar between the 2 groups. (16)

Clinical Studies with Advair HFA in Asthma

Adult and Adolescent Patients with Asthma

Advair HFA 115/21

Nathan et al (127) conducted 12-week, multicenter, randomized, double-blind, parallel group, placebo-controlled trial comparing *Advair HFA* 230/42 , salmeterol CFC 42 mcg, and fluticasone propionate CFC 220 mcg. The study evaluated 365 adult and adolescent patients with mild to moderate persistent asthma (mean FEV_1 = 68-69% of predicted) previously treated with moderate doses of inhaled corticosteroids. Morning plasma cortisol with short ACTH stimulation testing and 24-hour urine collection for urine cortisol were performed at baseline and endpoint in a subset of patients. At endpoint, there were no significant differences between treatment groups in plasma or urinary cortisol concentrations.

Advair HFA 230/21

A 12-week multicenter, randomized, double-blind, parallel-group comparison of *Advair HFA* 460/42 versus *Advair Diskus* 500/50 versus FP CFC 500 mcg alone was conducted in 509 adolescents and adults with moderate to severe asthma (mean FEV_1 = 71-74% of predicted) who were symptomatic on their current ICS therapy.(128) To assess hypothalamic-pituitary-adrenal (HPA) axis function at baseline and endpoint, fasting plasma cortisol levels in all patients and 24-hour urinary cortisol levels from a subgroup of patients were obtained. There was a significant difference in serum cortisol levels (P = 0.014) between *Advair HFA* 460/42 and *Advair Diskus* 500/50 at week 12, but not between *Advair HFA* 460/42 and FP CFC 500 mcg. There were no significant differences in urinary cortisol excretion between the groups.

One Year Study with *Advair HFA*

In a 12-month, open-label study, the safety and efficacy of *Advair HFA* 45/21 mcg, 115/21 mcg, and 230/21 mcg was evaluated in 325 adolescents and adults with asthma.(175) Patients 12 years of age or older with

a diagnosis of asthma requiring as-needed short-acting beta$_2$-agonist, long-acting beta$_2$-agonist and/or inhaled corticosteroids were randomized. In a subset of patients, 24-hour urinary cortisol levels were obtained to assess HPA axis function. Small decreases in urinary cortisol excretion were seen at the two higher doses; however, few patients experienced levels below the normal range.

Pediatric Patients with Asthma - Advair HFA 50/25 (ex-valve strength)

The safety of *Advair HFA* 50/25 (ex-valve strength) two inhalations twice daily was compared to that of fluticasone propionate (FP) HFA inhalation aerosol 50 mcg (ex-valve strength) two inhalations twice daily in a multicenter, randomized, double-blind, double-dummy, parallel group study in 350 children with persistent asthma ages 4 to 11 years.(67)

The values for 24-hour urinary cortisol excretion at baseline and after 12 weeks of treatment were similar between treatment groups. A summary of the 24-hour urinary cortisol excretion is provided in Table 31. Results show the addition of salmeterol to FP had no additional effect on urinary cortisol excretion although urinary cortisol values decreased in both treatment groups.

Table 31. 24-hour Urinary Cortisol Excretion

	Advair HFA **n=147**	**FP** **(n=144)**
Baseline (Geometric mean)	32.71	30.88
Week 12 (Geometric mean)	25.03	23.17
Geometric mean ratio (Week 12/Baseline)	0.77	0.75
Patients with abnormally low cortisol excretion at Baseline, n (%)	1 (<1%)	0
Patients with abnormally low cortisol excretion at Week 12, n (%)	2 (1%)	0

6.5 Studies Assessing Effect of *Advair* on Bone Mineral Density and Fracture Risk

Clinical Experience with Advair in Adults and Adolescents with Asthma

Controlled clinical trials examining the effects of *Advair* on bone metabolism and bone mineral density in patients with asthma have not been conducted; however, there was no evidence that treatment with *Advair* was associated with an increased risk of fractures during U.S. and non-U.S. clinical trials in asthma. Only 1% of the 1,824 patients participating in the clinical trials with *Advair Diskus* reported fractures, which were all considered unrelated to study treatment.(18,20,139,140,141) Less than 1% of the 2,339 patients participating in the clinical trials and long-term safety study with *Advair HFA* reported fractures, none of which were considered related to the study treatment.(142,143,144,145,175,176)

Clinical experience with Fluticasone Propionate Alone in Adults with Asthma

Long-term studies (>1 year)

Fluticasone Propionate Metered Dose Inhaler (MDI) vs. Placebo

A two-year multicenter, randomized, double-blind, parallel group trial compared the effects of two doses of FP MDI (88 mcg BID, n = 55) (440 mcg BID, n = 51) on BMD and bone metabolism to placebo (n = 54) in patients with mild asthma and minimal pre-study exposure to corticosteroids. (177) (178) Bone mineral density was analyzed by dual-energy X-ray absorptiometry (DEXA) measurements of the lumbar spine, proximal femur and total body every six months. All scans were compared with baseline measurements. Additionally, bone metabolism was measured using clinical laboratory data on serum osteocalcin every six months. At week 104, mean BMD at the 3 skeletal sites did not differ among groups ($P > 0.20$). There was no significant difference between groups in mean percent change from baseline in lumbar spine BMD: +0.21, +0.68, and -0.28 for placebo, FP 88 mcg BID and FP 440 mcg BID, respectively. For bone metabolism at week 104, mean serum osteocalcin values declined slightly in all treatment groups: -5.5, -4.1, -5.9 ng/mL ($P > 0.20$) for placebo, FP 88 mcg BID and FP 440 mcg BID, respectively. There were no skeletal fractures in any group during the two-year trial.

Fluticasone Propionate MDI vs. Beclomethasone

Egan, et al [179] compared the effects of FP inhalation aerosol (500 mcg twice daily) and inhaled beclomethasone dipropionate (BDP) (1000 mcg twice daily) on bone mineral density and biochemical markers of bone metabolism in a two-year, double-blind, parallel-group study. Thirty-three adult asthmatic patients with expected stable peak bone mass (males aged 18-50 years; pre-menopausal females aged 18-40 years) participated in the study; twenty-four patients completed the two-year study. The patients had previously received 1000-2000 mcg/day of an inhaled corticosteroid (BDP or budesonide) and had received no systemic corticosteroids within the previous two months; no patient had received more than two courses of systemic corticosteroids within the previous 12 months. Three open control groups were also followed over the two-year study: patients with mild asthma receiving low dose (≤ 400 mcg/day) inhaled corticosteroids (n = 16); patients with chronic, severe asthma receiving ≥ 10 mg/day of oral corticosteroids and high dose inhaled corticosteroids (mean 1500 mcg/day; n = 8); and healthy volunteers (n = 7).

Bone mineral density was measured at 0, 6, 12, and 24 months using quantitative computed tomography (QCT) of vertebral trabecular spine (both single and dual energy low-dose scanning techniques), single-photon absorptiometry (SPA) of forearm, and DEXA of lumbar spine, femoral neck, and whole body. Markers of bone formation (serum osteocalcin, bone alkaline phosphatase, procollagen type I C-terminal propeptide) and bone resorption (urine C-telopeptide of type I collagen and free deoxypyridinoline relative to creatinine) were measured every three months.

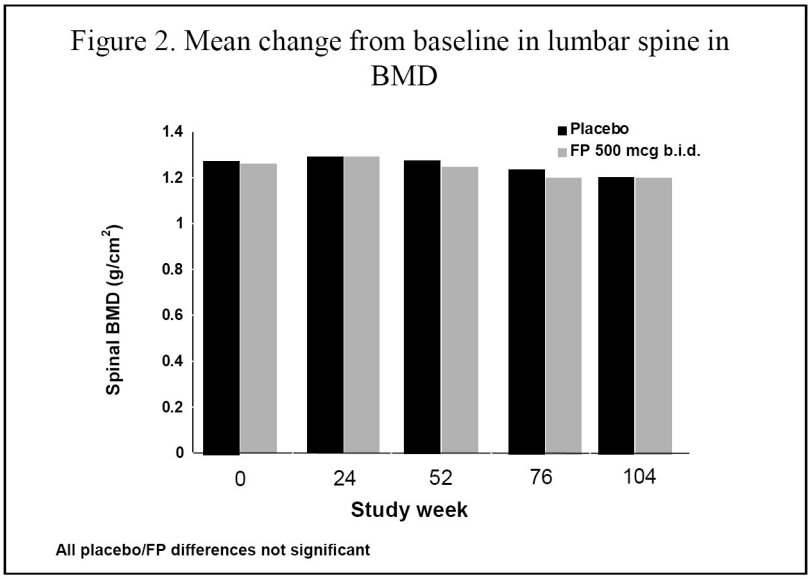
At baseline, BMD was lower in patients receiving inhaled corticosteroids (both low and high dose) than in healthy volunteers. Mean vertebral trabecular BMD with single energy QCT remained stable with no evidence of decline in patients who received FP. In contrast, a decline was observed in patients treated with BDP. This treatment difference between FP and BDP was statistically significant in favor of FP for QCT after 12 month and 24 months ($P < 0.01$). Similar results were observed with dual energy QCT, suggesting that the changes observed were due to changes in bone mineral and not due to changes in marrow fat. No significant changes in other measures of bone mineral density (SPA and DXA) or markers of bone metabolism were observed. The authors concluded that long-term changes over 24 months in BMD in patients on high-dose inhaled corticosteroids are minimal.

Fluticasone Propionate Dry Powder Formulation (Diskhaler) vs. Placebo

A two year study [180] was conducted to assess the effects of fluticasone propionate on the skeletal systems of 64 adult patients (males aged 18-50 years; pre-menopausal females aged 18-40 years) with mild persistent asthma. In this double-blind, parallel-group, placebo-controlled prospective trial, patients were randomized to receive fluticasone propionate 500 mcg twice daily via Diskhaler or placebo twice daily for 104 weeks (2 years). Bone mineral density measurements of the lumbar spine were performed using DEXA. Biochemical markers of bone formation and resorption (serum osteocalcin and urine N-telopeptide) were also evaluated at screening and every six months.

No significant differences were detected between groups for bone mineral density or biochemical markers of bone formation or resorption (Figure 18). Two patients in the placebo group and three in the fluticasone propionate group showed a ≥ 5% decrease in bone mineral density from baseline; however, only one patient (fluticasone propionate group) was withdrawn per pre-determined protocol after repeat scans.

Figure 18. Mean Change from baseline in lumbar spine BMD with FP 500 mcg BID vs. PBO



Clinical Experience with Advair in Children with Asthma

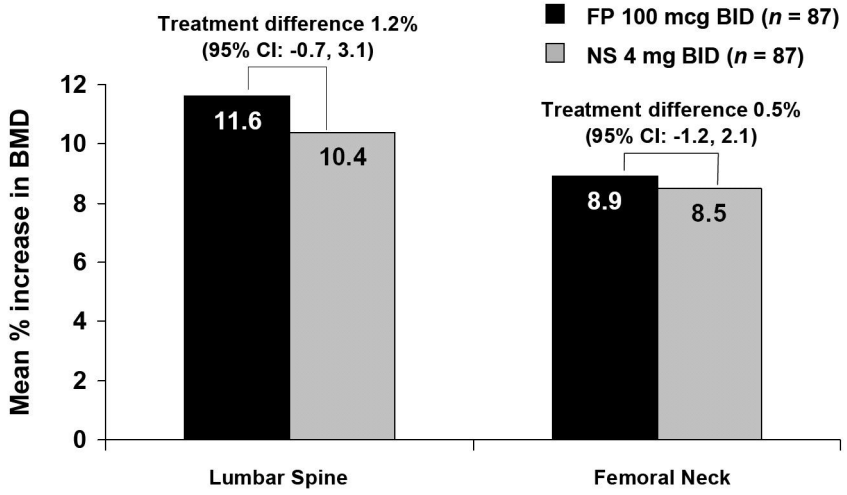
Controlled clinical trials examining the effects of *Advair* on bone metabolism and osteoporosis in patients with asthma have not been conducted; however, there was no evidence that treatment with *Advair* was associated with an increased risk of fractures during clinical trials in children.

Clinical Experience with Fluticasone Propionate Alone in Children with Asthma

Long-term studies (> 1 year) in children

Roux, et al [181] conducted a 24-month, randomized, open-label, multicenter, parallel-group study in 174 children 6-14 years of age with mild to moderate persistent asthma comparing the effect of fluticasone propionate (FP) inhalation powder (*Diskus* device) 200-400 mcg/day (n = 87) and nedocromil sodium (NS) 8-16 mg/day (n = 87) on bone mineral density (BMD). Dual-energy X-ray absorptiometry (DEXA) measurements of lumbar spine and femoral neck were recorded at baseline, 6, 12 and 24 months. At month 24, the adjusted mean percentage increase in lumbar spine BMD was 11.6% and 10.4% (95% CI for treatment difference: -0.7% - 3.1%) in the FP and NS groups, respectively. The corresponding increases in femoral neck BMD were 8.9% in the FP group and 8.5% in the NS group (95% CI: -1.2%-2.1%).

Figure 19. Increase in Bone Mineral Density after 24 months with FP or Nedocromil Sodium



Eid, et al[182] studied the effects on lumbar spine bone mineral density (BMD) of low dose FP ≤ 440 mcg/day and high dose FP > 440 mcg/day in 64 moderate to severe asthmatic children (37 males and 27 females). The BMD of patients (mean age 11.75 ± 3 years) was determined by DEXA after an average treatment time of 14 ± 4.9 months of therapy. The authors reported that 16% of patients exhibited osteoporosis, 37% had osteopenia, and 47% were normal. In patients receiving high-dose FP, males had a higher incidence of osteopenia or osteoporosis than females (52% versus 23%, respectively, $P = 0.049$). There were no significant differences in the low-dose FP group between males and females. For all patients, males were more prone to losses in BMD than females (54% versus 25.9%, respectively, $P = 0.013$).

Gregson, et al [183] conducted a double-blind, randomized, parallel-group study in 23 steroid-naïve, prepubescent children (15 boys, 8 girls) aged 5-10 years (mean age = 6.7 years) with moderately severe asthma to investigate the effects of FP and BDP on bone mineral density. Children were randomized to treatment with FP 100 mcg twice daily or BDP 200 mcg twice daily for 20 months (inhalation device not defined). DEXA scans were performed regularly throughout the study to measure BMD. Densitometry of lumbar spine and total body showed a significant increase over time that followed the normal increases in density with age. There was no difference between the two treatment groups. In addition, there was no change in fat distribution over time and no increase in the percentage of total body fat.

A 2-year, randomized, double-blind study in 55 children with asthma evaluated the dose-dependent effects of FP on bone metabolism. [184] Children were 6-10 years of age with mild-to-moderate persistent asthma who were previously receiving inhaled corticosteroids. Children were randomized to receive either FP inhalation powder 200 mcg/day at a constant dose for 2 years (n = 27) or a high starting dose of FP 1000 mcg/day for 6 months followed by reductions every 2 months to 500, 200 and 100 mcg/day (n = 28) during the remaining 18 months. Markers of bone metabolism and BMD were similar at baseline. Serum osteocalcin, serum P1NP, and urinary Dpyr (deoxypyridinoline) decreased significantly during treatment with FP 1000 and 500 mcg/day compared with 200 mcg/day. Similar serum osteocalcin levels were observed when both groups received 200 mcg/day or 200 mcg/day and 100 mcg/day. Urinary Dypr and serum P1NP were significantly higher among step-down patients receiving 100 mcg/day at month 18 compared with patients receiving a constant dose of 200 mcg/day. No significant differences between groups were seen in BMD after 2 years. The authors concluded that dose-dependent biochemical bone turnover was found with 1000 and 500 mcg/day compared with 200 mcg/day.

Clinical Experience with Advair Diskus in Patients with COPD

Advair Diskus 250/50 Three-Year Study

A multi-center, randomized, double-blind, parallel-group study was conducted to compare *Advair Diskus 250/50* twice daily with salmeterol 50 mcg twice daily for 3 years in patients with COPD.[162] The study was designed to evaluate the effects of the fluticasone propionate component of *Advair* compared with the effects of the salmeterol component on BMD. BMD was measured in the lumbar spine and total hip by dual energy x-ray absorptiometry (DEXA) at baseline, 26, 52, 78, 104, 130 and 156 weeks. Male and female patients ≥40 years of age who were current or former smokers with a ≥10 pack-year history and a diagnosis of COPD were enrolled. Inclusion criteria included a baseline FEV_1 of <70% of predicted and FEV_1/FVC of ≤0.7. Patients receiving oral corticosteroids for >6 weeks, bisphosphonates, calcitonin, or parathyroid hormone analogues within the prior year, or patients with a history of metabolic bone disease were excluded.

The primary study endpoint was the change in BMD in the lumbar spine in patients who were at least 50% compliant with study medications and who had a post-baseline DEXA scan. The primary analysis was to test for clinical equivalence. A summary of the baseline characteristics of the patients appears in Table 32.

Table 32. Baseline Characteristics

	Advair Diskus 250/50 **(n=82)**	**Sal 50 mcg (n=84)**
Mean age (yr)	66	66
Males (%)	60	63
Caucasian (%)	96	99
Mean BMI	27.8	27.6
Mean BMD lumbar spine	1.06	1.09
Mean BMD total hip	0.92	0.90
BMI=body mass index; Sal=salmeterol; yr= years		

Equivalence was not established for lumbar spine BMD, although the results numerically favored *Advair Diskus 250/50* . Clinical equivalence was established for total hip BMD with *Advair* 250/50 compared with salmeterol 50 mcg. A summary of the results appears in Table 33. The rate of bone fractures was low in both treatment groups. Six patients receiving *Advair* and 3 patients receiving salmeterol reported a bone fracture during the study. There were 1 and 3 traumatic fractures and 7 and 1 non-traumatic fractures in the *Advair* and salmeterol groups, respectively.

Table 33. Change in BMD with *Advair Diskus* 250/50 at 3 Years (Week 156)

	Advair Diskus 250/50 **(n=57)**	**Sal 50 mcg (n=51)**
Lumbar Spine		
Mean % change from Baseline	1.9	0.3
Slope difference, *Advair*-Sal (%/year)	0.8 (0.06, 1.49)*	
Total Hip		
Mean % change from Baseline	-2.9	-1.8
Slope difference, *Advair*-Sal (%/year)	-0.3 (-0.78, 0.24)	
*95% CI bounds of ±1% was used to determine clinical equivalence. Models for BMD adjusted for baseline BMD, investigator, sex, age, BMI, FEV_1, baseline activity, calcium supplements, and smoking status. BMD=bone mineral density; CI=Confidence Interval; Sal=Salmeterol		

The TORCH Study – *Advair Diskus* 500/50 Three-Year Study

The TORCH (TOwards a Revolution in COPD Health) study was a three-year, randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational study.[48] Patients with chronic obstructive pulmonary disease (COPD) (prebronchodilator forced expiratory volume in one second [FEV_1] <60% of predicted) were randomized to three-years of twice-daily treatment with either *Advair Diskus* 500/50, fluticasone propionate (FP) 500 mcg, salmeterol 50 mcg, or placebo. The primary endpoint was all-cause mortality.

A safety study was conducted in a subset of patients (n=658) to assess the effect of *Advair Diskus 500/50* on bone mineral density. In these patients, a DEXA scan was conducted at baseline, and at weeks 48, 108, and 158 weeks. BMD was measured at the total hip, and L_1-L_4 regions of the lumbar spine. At 3 years, there was no significant difference between active treatments and placebo in the percent change in BMD of the total hip or the lumbar spine (Table 34).

Table 34. Change in BMD with *Advair Diskus 500/50* at 3 Years (Week 158)

	Advair Diskus 500/50 **(n=165)**	**FP 500 mcg (n=163)**	**Sal 50 mcg (n=166)**	**Placebo (n=164)**
Total Hip				
No. at Week 158	82	65	78	52
Adjusted % Change from Baseline	-3.2	-2.9	-1.7	-3.1
Lumbar Spine				
No. at Week 158	81	63	76	50
Adjusted % Change from Baseline	-0.3	-0.3	1.5	0.0
FP=fluticasone propionate; Sal=Salmeterol				

The risk of fracture was evaluated across the entire safety population. There was no significant difference in the probability of having a bone fracture between treatments (Table 35).

Table 35. Incidence of Fractures with *Advair Diskus 500/50* Over 3 Years

	Advair Diskus 500/50 **(n=1546)**	**FP 500 mcg (n=1522)**	**Sal 50 mcg (n=1542)**	**Placebo (n=1544)**
All, %	6.3	5.4	5.1	5.1
Nontraumatic, %	1.7	1.7	2.5	1.8
FP=fluticasone propionate; Sal=Salmeterol				

6.6 Studies Assessing Effect of *Advair* on Growth

Clinical Studies with Advair on Growth

There are no studies evaluating the effect of *Advair Diskus* or *Advair HFA* on growth.

Impact of Fluticasone Propionate (FP) on the Attainment of Final Height

Controlled clinical studies have shown that orally inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients.(68) This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for 'catch up' growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

Inhaled corticosteroids, including fluticasone propionate, a component of *Advair Diskus* and *Advair HFA*, may cause a reduction in growth velocity in children and adolescents. The growth of pediatric patients receiving orally inhaled corticosteroids, including *Advair Diskus* and *Advair HFA*, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including *Advair Diskus* and *Advair HFA*, each patient should be titrated to the lowest strength that effectively controls his/her asthma.

Several long-term clinical studies have demonstrated that most children 4 to 11 years old had growth rates in the normal range at recommended doses of inhaled fluticasone propionate. (185) (186) (187) (188) (189) The studies followed growth for 1 to 2 years. A 1-year study found that in a subset of children who remained prepubertal, growth rates were 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the FP 50 mcg group (n = 74), and 5.67 cm/year in the FP 100 mcg group (n = 79). In children 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is: boys - 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year.(68)

7. COMPARATIVE DATA

7.1 Comparison with Concurrent Use of Fluticasone Propionate and Salmeterol in Asthma

Clinical Trials In Adults

Advair Diskus 100/50 vs. Concurrent Salmeterol 50 mcg and Fluticasone Propionate 100 mcg

Bateman, et al conducted a multicenter, randomized, double blind, double-dummy, parallel-group trial to determine clinical equivalence of *Advair Diskus* 100/50 and the concurrent use of fluticasone propionate (FP) 100 mcg via *Diskus* and salmeterol 50 mcg via *Diskus* in patients who were symptomatic despite the use of inhaled corticosteroids. [17,18] Prior to entering the study, patients were receiving treatment with FP 200-250 mcg/day or budesonide or beclomethasone dipropionate 400-500 mcg/day. A total of 244 patients with mild to moderate asthma [mean baseline forced expiratory volume in one second (FEV_1) = 75-76% of predicted] were randomized to treatment with either *Advair Diskus* 100/50 twice daily or concurrent use of FP 100 mcg twice daily via *Diskus* and salmeterol 50 mcg twice daily via *Diskus* for 12 weeks. All patients received as needed albuterol. The primary efficacy parameter was mean morning peak expiratory flow (PEF). The treatments were deemed equivalent if the 90% confidence interval (CI) fell within +15 L/min.

Over weeks 1-12, both treatments improved morning PEF with adjusted mean change from baseline values of 42 L/min and 33 L/min for *Advair Diskus* 100/50 and concurrent therapy, respectively, with no statistical differences between groups. However, the two treatments failed to meet the equivalence criterion with a treatment difference of –9 L/min and a 90% CI of –17 to 0 L/min over weeks 1 to 12. Improvements in FEV_1 were observed in both the *Advair Diskus* 100/50 and concurrent use groups with adjusted mean changes from baseline of 0.20 L (6%) and 0.17 L (6%), respectively. No significant differences were seen in all other secondary endpoints (Table 36). Both treatments were well-tolerated throughout the 12-week period. No difference was seen between groups in geometric mean morning serum cortisol.

Table 36. *Advair Diskus* 100/50 versus FP 100 mcg plus Salmeterol 50 mcg: Secondary Endpoints*

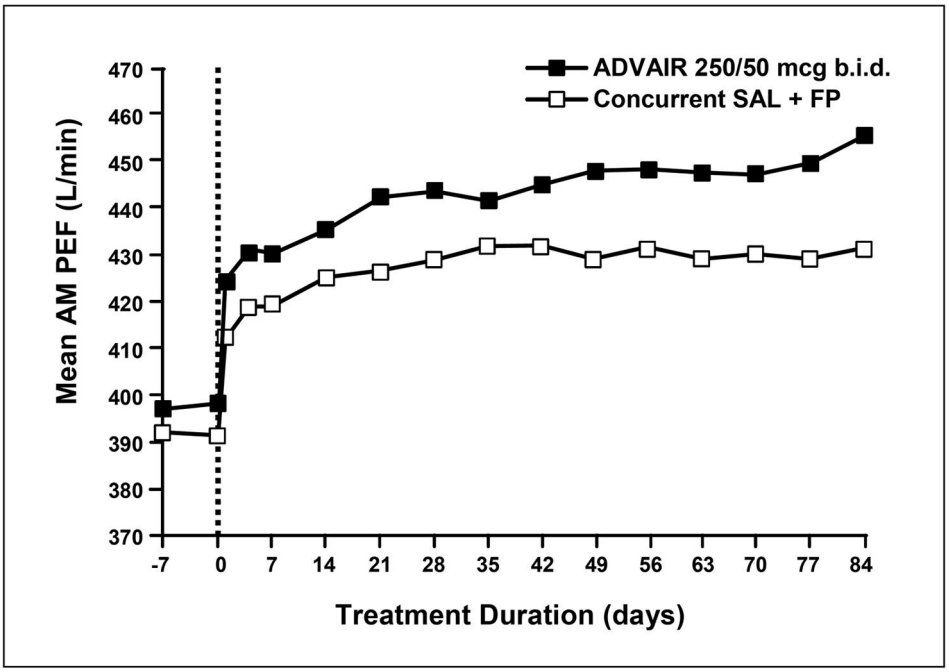
	Advair Diskus	**FP + Salmeterol**
Mean Change In PM PEF (L/Min) From Baseline Over Weeks 1-12	36	30
Median % Of Days With No Symptoms Over Weeks 1-12	61	68
Median % Of Nights With No Symptoms Over Weeks 1-12	80	82
Median % Of Days With No Albuterol Use Over Weeks 1-12	76	83
Mean Change From Clinic FEV_1 (L) From Baseline At Week 12	0.2	0.17
*No significant differences between groups		

Advair Diskus 250/50 vs. Concurrent Salmeterol 50 mcg and Fluticasone Propionate 250 mcg

Chapman, et al performed a multicenter, double-blind, double-dummy study to determine the equivalence of *Advair Diskus* 250/50 versus the concurrent use of FP 250 mcg plus salmeterol 50 mcg in adults with mild to moderate asthma (FEV_1 = 75-77% of predicted) that was symptomatic despite use of inhaled corticosteroids. [19,20] Prior to randomization, patients were receiving treatment with either FP 400-600 mcg/day or beclomethasone dipropionate or budesonide 800-1200 mcg/day for at least 4 weeks. After a two week run-in period, patients were randomized to treatment with either *Advair Diskus* 250/50 twice daily or the concurrent use of FP via *Diskus* 250 mcg twice daily plus salmeterol via *Diskus* 50 mcg twice daily for 28 weeks. All patients had access to as-needed albuterol. During the first 12 weeks of therapy, efficacy data was collected. The primary efficacy parameter was mean morning PEF. Safety data was gathered throughout the entire 28 weeks.

Over weeks 1-12, *Advair Diskus* 250/50 and concurrent therapy improved morning PEF with adjusted mean changes from baseline of 43 and 36 L/min, respectively (Figure 20).

Figure 20. Mean Morning PEF at Baseline and Over 12 Weeks



The difference between the treatment groups for mean change in PEF was –6 L/min, with a 90% CI (-13 to 0 L/min) which met the pre-defined equivalence definition of ±15 L/min. Evening PEF also improved with adjusted mean changes from baseline of 35 and 25 L/min for *Advair Diskus* 250/50 and concurrent therapy, respectively.

No significant differences were observed between groups for any secondary efficacy measures (Table 37). Both treatments were well-tolerated throughout the 28 week period. Before and during treatment, mean serum cortisol concentrations were not significantly different between groups.

Table 37. *Advair Diskus* 250/50 versus FP 250 mcg Plus Salmeterol 50 mcg: Secondary Endpoints*

	Advair Diskus	**FP + Salmeterol**
Mean Change In PM PEF (L/min) From Baseline Over Weeks 1-12	35	25
Median % Of Days With No Symptoms Over Weeks 1-12	22	16
Median % Of Nights With No Symptoms Over Weeks 1-12	74	60
Median % Of Days With No Albuterol Use Over Weeks 1-12	67	52
Mean Change From Clinic FEV_1 (L) From Baseline At Week 12	0.21	0.21
*No significant differences between groups		

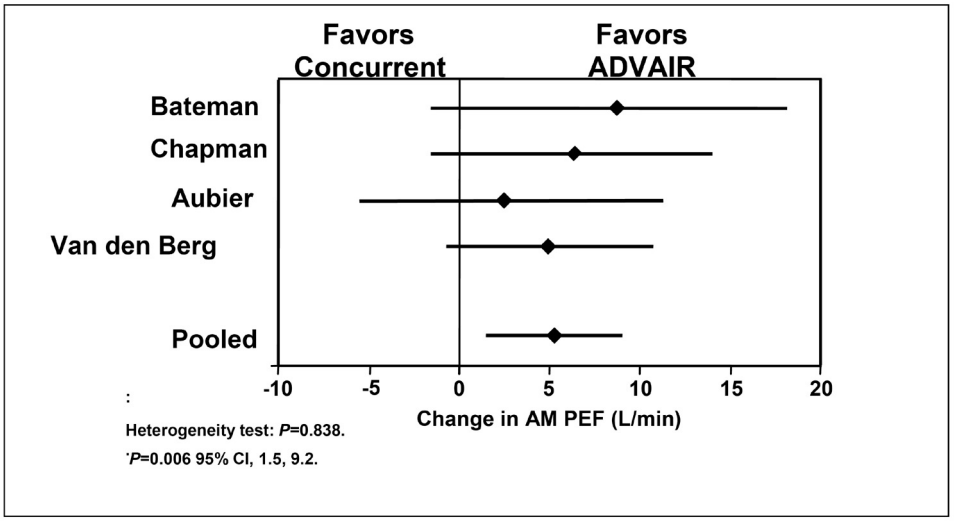
Meta-Analysis

Nelson, et al [21] conducted a meta-analysis of four studies described above [17] [19] [9] [118] in order to explore the complementary actions of FP and salmeterol. All studies were randomized, double-blind, double-dummy studies. Individual patient data from these studies were combined to provide overall estimates of treatment effect for morning PEF and the other efficacy measures.

Individually, each of these studies demonstrated comparable efficacy between *Advair Diskus* and concurrent therapy on the basis of morning PEF. However, there was a clear and consistent trend in favor of *Advair Diskus* over concurrent therapy. The results of the meta-analysis showed a significant improvement (Figure 21) of 5.4 L/min ($P = 0.006$; 95% confidence interval [CI], 1.5-9.2) in morning PEF from baseline for patients treated with *Advair Diskus* compared with concurrent therapy over the 12-week treatment period. Logistic regression analysis showed that the odds of achieving a >15 or >30 L/min improvement in morning PEF with *Advair Diskus* were increased by approximately 40% compared with concurrent treatment (15 L/min: odds ratio=1.42; $P = 0.008$, 95% CI = 1.1-1.8; 30 L/min: odds ratio = 1.40, $P = 0.006$, 95% CI = 1.1-1.8). These values represent an additional 7-9% and 5-14% more patients treated with *Advair Diskus* having a >15 and >30 L/min improvement, respectively, compared with

concurrent treatment. The difference in evening PEF (6.11 L/min; $P < 0.001$) also significantly favored *Advair Diskus* over concurrent treatment. The mean difference in FEV_1 was 40 ml in favor of *Advair Diskus*, but the difference was not significant ($P = 0.054$). There were no significant differences between groups in the percentage of symptom-free and albuterol-free days and nights.

Figure 21. Mean Change in AM PEF



Thus, the meta-analysis demonstrated that FP plus salmeterol delivered from a single device as *Advair Diskus* may potentially result in increased clinical efficacy compared with concurrent use FP plus salmeterol at the same dose administered separately in different devices. After administration from a single inhaler, FP and salmeterol may co-deposit in the airways. Co-deposition may offer an increased opportunity for a synergistic interaction to occur.

7.2 Comparison with Budesonide Formoterol Combination in Asthma

Busse et al.

A 7-month randomized, open-label study compared the efficacy and safety of stable doses (SD) of budesonide formoterol combination (BFC) 160/4.5 mcg (2 inhalations twice daily) via metered-dose inhaler (MDI), stable doses of *Advair Diskus* 250/50 (1 inhalation twice daily), and adjustable maintenance dosing (AMD) of BFC 160/4.5 mcg (2 inhalations daily to 4 inhalations twice daily) via MDI.[22] Patients (N = 1225) who were ≥ 12 years of age with moderate to severe asthma (forced expiratory volume in 1 second [FEV_1] ≥ 50 % predicted) previously treated with inhaled corticosteroids with or without a long-acting $beta_2$-agonist were enrolled. Patients remained on their current therapy for the 10- to 14-day run-in period and were then randomized 2:1 to stable doses of BFC 160/4.5 mcg (2 inhalations twice daily) or *Advair Diskus* 250/50 (1 inhalation twice daily) [Treatment Period 1] if they met the following criteria: FEV_1 ≥ 50% of predicted; ≥ 8 inhalations of albuterol during last 10 days of run-in; and mean morning peak expiratory flow (PEF) for the last 7 days of the run-in period of 50% to 85% of the value at screening.

After 1 month, patients receiving stable doses of BFC were randomized 1:1 to adjustable maintenance dosing with BFC or remained on a stable dose of BFC for 6 months [Treatment Period 2]. Patients previously receiving stable doses of *Advair Diskus* remained on *Advair Diskus* for an additional 6 months. Therapy for patients in the BFC AMD treatment arm could be stepped up or stepped down based on specific criteria. Patients who experienced 2 or more consecutive days with ≥ 6 inhalations/day of rescue medication or nighttime awakenings due to asthma were stepped-up from 2 inhalations daily or twice daily to 4 inhalations twice daily. After 7 days of step-up treatment, therapy could then be stepped back down to their previous regimen of 2 inhalations daily or twice daily if on the last 2 consecutive days patients had ≤ 2 inhalations of rescue medication and no nighttime awakenings due to asthma. In addition, therapy could be stepped down from 2 inhalations twice daily to 2 inhalations daily at randomization or after 3 months of treatment if in the previous 7 days patients had ≤ 2 inhalations/day of rescue medication for ≤ 2 days and no nighttime awakenings due to asthma.

Baseline characteristics of randomized patients were similar between treatment groups. Patients were approximately 39 years of age with a mean FEV_1 of 78-79% predicted at randomization. The mean total ICS dose at study entry was between 539 to 556 mcg/day. The primary endpoint was exacerbations which was defined as worsening asthma requiring oral corticosteroids.

There were no significant differences among treatment groups in the percentage of patients with ≥ 1 exacerbation or in the total number of exacerbations per patient-treatment year during the overall randomized treatment period, treatment period 1, or treatment period 2 (Table 38). In addition, there were no significant differences for the time to first exacerbation during the overall treatment period. Improvements in FEV_1 and morning PEF were similar between treatment groups for the overall randomized treatment period.

Table 38. Effects on Exacerbations and Lung Function

	***Advair Diskus* SD** **n = 404**	**BFC SD** **n = 422**	**BFC AMD** **n = 389**
Exacerbations			
≥1 exacerbation, n (% of patients)	37 (9.2)	37 (8.8)	31 (8.0)
Exacerbations per patient-treatment year	0.189	0.24	0.196

In addition, improvements in asthma symptoms, rescue medication use, and lung function were similar across treatment groups for the overall treatment period.

The incidence of adverse events were similar among treatment groups. In addition, there were no significant differences or clinically relevant changes in pulse rate, systolic and diastolic blood pressures for any treatment group.

EXCEL Study

A 24-week, randomized, double-blind, double-dummy, multicenter study was conducted in 1391 patients ≥18 years, with persistent asthma who were symptomatic on 1000-2000 mcg/day of ICS (beclomethasone diproprionate or equivalent) alone.[23] At the screening visit, patients were required to demonstrate a reversible increase in forced expiratory volume in 1 second (FEV_1) of ≥12% after inhaling albuterol 200-400 mcg. Combination therapy, if used, was discontinued and replaced with ICS alone, at least 4 weeks prior to the study start. Following a 2-week run-in period, patients who remained symptomatic (reversible increase in FEV_1 ≥12% [and ≥200mL] and an asthma symptom score ≥2 on ≥4 of the last 7 days) were randomized to treatment with *Advair Diskus* 250/50 one inhalation twice daily (n=694), or budesonide formoterol combination (BFC) via Turbuhaler 200/6 mcg two inhalations twice daily (n=697) for 24 weeks. Baseline demographics between treatment groups were similar.

The primary endpoint was the adjusted mean rate of all exacerbations over the 24-week treatment period. Exacerbations were assessed from the patient's daily record card by the physician at each scheduled visit (Table 39). Patients in the *Advair Diskus* 250/50 and BFC groups had similar rates of exacerbations (2.69 and 2.79, respectively, *P*=NS) [Table 40]. The majority of exacerbations were mild. After adjusting for time interval, there was a significant effect of time, such that the rate across both treatment groups showed a 30% reduction in weeks 9-16 (95% CI: 24-36%; *P*<0.001) and a 36% reduction in weeks 17-24 (95% CI: 30-42%; *P*<0.001), compared with weeks 1-8. There were more moderate/severe exacerbations in the BFC group than in the *Advair Diskus* group (80 vs. 67, respectively). A post-hoc analysis showed that over weeks 1-24, patients treated with *Advair Diskus* experienced a 30% lower rate of moderate/severe exacerbations compared with those treated with BFC (*P*=0.059). During weeks 17-24, the rate of moderate/severe exacerbations was 57% lower in the *Advair Diskus* compared with the BFC group (0.105 vs. 0.244, respectively, *P*=0.006).

Table 39. Exacerbation Definitions

Severity	Definition
Mild	• Morning peak expiratory flow (PEF) >20% below baseline (mean of last 7 days of run-in) for ≥2 consecutive days OR • More than 3 additional reliever occasions/24 hour period with respect to baseline for ≥2 consecutive days OR • Awakenings at night due to asthma for ≥2 consecutive nights
Moderate	Deterioration in asthma requiring treatment with oral prednisone 40-60 mg/day for 7-10 days. Either: • Morning PEF >30% below baseline (mean of last 7 days of run-in) for ≥2 consecutive days OR • A clinical deterioration assessed by investigating physician as requiring oral steroid treatment
Severe	• Deterioration in asthma requiring hospital admission.

Table 40. Summary of Exacerbations

	***Advair Diskus* 250/50 (n=694)**	**BFC 200/6 mcg (n=697)**	***P*-value**
Mean rate over 24 weeks	2.69	2.79	0.571
Rate of moderate/severe exacerbations (adjusted mean rate/year)			
Weeks 1-24	0.155	0.223	0.059
Weeks 1-8	0.227	0.224	0.960
Weeks 9-16	0.157	0.202	0.371
Weeks 17-24	0.105	0.244	0.006
Severity of exacerbations, n (% of patients)			
No exacerbations	258 (37)	246 (35)	
Mild exacerbations	369 (53)	371 (53)	
Moderate/Severe Exacerbations	67 (10)	80 (11)	

Other efficacy endpoints included morning PEF, FEV_1, % symptom-free days and nights, and % of rescue-free days. Both treatment groups improved in all of these endpoints, but there were no statistically significant differences between the groups (Table 41).

Table 41. Lung Function and Patient-Rated Data

Parameter	***Advair Diskus* (n=694)**	**BFC (n=697)**
Morning PEF (L/min)		
Baseline (mean)	357.5	348.3
Adjusted mean change	41.8	41.4
FEV_1 (L)		
Baseline (mean)	2.43	2.40
Adjusted mean change	0.29	0.27
% symptom-free days		
Baseline (median)	0	0
Weeks 1-24 (median)	63	60
% symptom-free nights		
Baseline (median)	14	25
Weeks 1-24 (median)	85	96
% rescue-free days		
Baseline (median)	0	0
Weeks 1-24 (median)	82	81
P=NS for all endpoints listed		

The proportion of patients who achieved a week of 'well controlled' asthma (Table 42) at any point during the study was the same in both treatment groups, 70%. Over weeks 1-24, the mean number of weeks with

'well-controlled' asthma was slightly higher in the *Advair Diskus* group than in the budesonide/formoterol group (10.2 vs. 9.6 weeks, *P*=0.391).

Table 42. Criteria for 'Well-Controlled' Asthma Week

Two or more of the following:
• A symptom score of >1 on no more than 2 days
• No more than 2 days of rescue albuterol use, up to a maximum of 4 occasions per week
• ≥80% predicted morning PEF every day
AND all of the following:
• No nighttime awakenings due to asthma
• No exacerbations
• No emergency visits
• No treatment-related adverse events (AE) enforcing a change in asthma therapy

Overall, both treatment groups were shown to be safe and well-tolerated. Both groups showed similar incidence and type of adverse events. The most commonly reported drug-related adverse events were hoarseness/dysphonia (*Advair Diskus*: 2%; BFC: 2%), candidiasis of the mouth/throat (*Advair Diskus*: 2%; BFC: 1%), and headaches (*Advair Diskus*: 1%; BFC: 2%).

COMPASS

A 6-month, randomized, multicenter, double-blind, double-dummy study compared the efficacy of BFC 160/4.5 mcg twice daily plus additional doses as-needed (n=1107) with higher stable doses of *Advair HFA* 125/25 two inhalations twice daily plus as needed terbutaline (n=1123) and BFC 320/9 mcg twice daily plus as-needed terbutaline (n=1105).[190] The study included symptomatic patients ≥ 12 years of age with asthma. Patients included had a mean FEV_1 of ≥50% predicted with ≥ 12% reversibility following terbutaline 1 mg and were receiving an ICS [≥500 mcg/day of budesonide or fluticasone (or ≥ 1000 mcg/day of another ICS) for ≥ 1 month] for ≥ 3 months prior to study entry. In addition, patients were enrolled if they had at least one or more asthma exacerbations in the previous 12 months. Following a 2 week run-in where patients remained on their current ICS, those patients requiring reliever medication on ≥5 of the last 7 days of the run-in were randomized to treatment. The primary study endpoint was time to first severe exacerbation.

Baseline characteristics were similar between the treatment arms. There was no significant difference in time to first severe exacerbation between the stable dose *Advair HFA* and stable dose BFC treatment arms. There was a significant difference in favor of *Advair HFA* in the total number of inhalations per day of rescue medication compared with stable dose BFC (*P*≤0.05). However, there were no significant differences between the two stable dose treatments in other secondary endpoints including asthma symptoms, nighttime awakenings, asthma control days, rescue-free days, number of mild exacerbations, the number of severe exacerbations and other measures of lung function.

All three treatments were well tolerated and there were no notable between-group differences in the number or the severity of the adverse events. The most commonly reported adverse events were upper respiratory tract infection, pharyngitis, and nasopharyngitis. Serious adverse events were reported in 3% of the stable dose *Advair HFA* group and 4% in the stable dose BFC group. A serious drug-related adverse event was reported by one patient in the *Advair HFA* group (asthma).

SAM40048

Advair Diskus 250/50 was compared to BFC 200/6 mcg via the Turbuhaler each administered twice daily for 12 weeks in a multicenter, randomised, double-blind, parallel group study in 248 adult patients with moderate asthma.[24] The primary study endpoint was the change in FEV_1 % predicted after 12 weeks. Inclusion criteria included FEV_1 50% to 80% of predicted, ≥15% FEV_1 reversibility, ICS treatment with 1000 mcg/day of beclomethasone diproprionate or equivalent and symptomatic asthma. The mean baseline FEV_1 % predicted was 64.8% for the patients treated with *Advair Diskus* and 65.6% for the patients treated with BFC. At week 12, these values had increased to 78.8% and 76.5%, respectively. The difference between treatments in mean change in FEV_1 % predicted was not significant (*P*=0.082). The mean proportion of days without symptoms increased from 10.4 to 37.3 for the patients treated with

Advair Diskus and from 16.9 to 37.5 for the BFC patients. The mean proportion of days without rescue medication increased from 12.5 to 37.8 for the patients treated with *Advair Diskus* and from 16.6 to 40.4 for the patients treated with BFC. Treatment emergent adverse events occurred in 36% of patients treated with *Advair Diskus* and in 31% of patients in the BFC group.

7.3 Comparison with a Higher Dose of Inhaled Corticosteroid in Asthma

Comparison of Advair Diskus with Higher Doses of FP in Adults

A randomized, double-blind, parallel-group study in Germany compared the efficacy and safety of *Advair Diskus* 250/50 twice daily with double the dose of inhaled corticosteroid (FP 500 mcg twice daily) in patients with asthma who were symptomatic on moderate doses of inhaled corticosteroid therapy.[25] Patients included in the study were 18-70 years of age, with a diagnosis of asthma for at least 6 months, who were being treated with 800-1000 mcg/day of beclomethasone dipropionate or budesonide or 500 mcg/day of FP. Patients were enrolled if their asthma was determined to be of moderate severity (asthma symptoms >twice/week but <once/day, nighttime symptoms >twice/month but <once/week, FEV_1 between 50-80% predicted, and ≥15% increase in FEV_1 from baseline following 200 mcg of inhaled albuterol).

During a 2-week screening phase, patients recorded symptoms and PEF while continuing their current asthma therapy. Only patients who were considered symptomatic (rescue medication use on ≥7 of 14 days, or asthma symptom score ≥10 points [sum of day and nighttime scores over 14 days]) were randomized to the 12-week double-blind treatment period with either *Advair Diskus* 250/50 twice daily or FP 500 mcg twice daily. The primary study endpoint was mean change in PEF between treatment groups.

A total of 365 patients were randomized to treatment. The intent-to-treat group consisted of 170 patients who received *Advair* and 177 patients received FP who had no critical protocol violation. Baseline demographics and characteristics were comparable between treatment groups. Mean age was approximately 49 years, mean FEV_1 was 75-76% of predicted and only 16-17% of days were free of asthma symptoms.

Patients receiving *Advair Diskus* had a significant improvement in PEF compared with FP as early as week 2 of therapy. At week 2, patients receiving *Advair Diskus* had a 37 L/min increase in PEF compared with 20 L/min increase with FP. Morning PEF increased further in the study, with a significant improvement in patients receiving *Advair Diskus* 250/50 compared with FP 500 mcg at Week 12 (see Table 43). Additionally, significant improvements in evening PEF, symptom scores, symptom-free days and albuterol use was observed in patients receiving *Advair Diskus* 250/50 compared with higher doses of FP. At week 12, FEV_1 increased by 12.3% of predicted in the *Advair* treatment group compared with 8.4% with FP; this difference was not statistically significant.

Table 43. Results: Change from Baseline at Week 12

	***Advair Diskus* 250/50 BID**	**FP 500 mcg BID**	**Adjusted Difference Between Groups (95% CI)**	***P*-value**
Morning PEF, L/min	52	36	16.6 (1.1, 32.0)	0.04
Evening PEF, L/min	46	29	18.1 (3.1, 33.0)	0.02
Symptom Score*	-1.5	-1.0	-0.5 (-0.78, -0.22)	0.0005
% Symptom-free Days	49	38	12.6 (4.0, 20.7)	0.004
Albuterol Use, puffs/day	-1.6	-1.0	-0.84 (-1.13, -0.37)	0.0001
FEV_1, L	0.36	0.25	-	NS

Values represent mean number unless otherwise specified

NS = non-significant

*score of 0 (none) to 4 (severe) for daytime and nighttime symptoms

A similar percentage of patients reported adverse event with *Advair* (26.3%) compared with FP (24.2%). The most common event was respiratory tract infection (12 in the *Advair* group and 25 in the FP group). There were four exacerbations with FP and 1 with *Advair*. Systolic and diastolic blood pressure as well as heart rate did not change significantly throughout the study.

Advair HFA Compared with Higher Doses of FP in Adult and Adolescent Patients

A 12-week, randomized, double-blind study in Canada compared *Advair HFA* 50/25 (comparable to *Advair HFA* 45/21 in the U.S.) two inhalations twice daily with FP 125 mcg two inhalations twice daily in patients symptomatic on low-dose FP (200 mcg/day or equivalent).[191,192] Patients were included in the study if they were 12 years of age or older with a documented history of reversible airway obstruction. To enter the 4 week open-label FP 200 mcg/day pre-baseline period, patients were required to have been symptomatic despite use of ≤ 500 mcg/day beclomethasone dipropionate, budesonide, or equivalent or have been using either FP at a dose < 200 mcg/day or using FP 200 mcg/day for less than 4 weeks. Patients who remained symptomatic at the end of the pre-baseline period were eligible to enter the 2-week baseline period during which time they continued to take open-label FP 200 mcg/day. Patients who had remained symptomatic despite already having used FP 200-250 mcg/day for ≥ 4 weeks could enter the baseline period without going through the pre-baseline period.

If after the 2-week baseline period patients remained symptomatic, they were eligible to continue into the treatment period. Patients with an FEV_1 of <60% or >90% of predicted normal values at the pre-baseline visit were excluded from the study, as were those demonstrating a PEF of <60% or >90% of their maximum achievable PEF measured. The primary endpoint was change from baseline in morning PEF.

The intent-to-treat population included 121 patients randomized to *Advair HFA* and 116 patients randomized to FP. Patient demographics were similar between treatment arms. As shown in Table 44 below, patients receiving *Advair* had a 13.7 L/min improvement in morning PEF over higher doses of FP alone. Significant improvements were also seen in evening PEF, symptom-free days and symptom-free nights in patients receiving *Advair* compared with FP. Numerical improvements in FEV_1 and increases in albuterol-free days were also observed in favor of patients receiving *Advair*; however, these differences did not reach statistical significance. Additionally, there was a smaller percentage of patients in the *Advair* group who had ≥1 asthma exacerbation than in the FP group (7.4% vs. 13.8%, $P = 0.117$).

Table 44. Results: Least Square Mean Change from Baseline at Endpoint

	***Advair HFA* 100/50 BID**	**FP 250 mcg BID**	**Treatment Difference (95% CI)**	***P*-Value**
AM PEF, L/min	44.4	30.7	13.7 (1.2, 26.2)	0.032
PM PEF, L/min	41.8	24.3	17.4 (3.8, 31.0)	0.004
FEV_1, L	0.172	0.157	0.015 (-0.079, 0.109)	NS
Symptom-free days, %	35.4	22.4	13 (3.8, 22.2)	0.006
Symptom-free nights, %	24.7	13.3	11.5 (2.8, 20.1)	0.01
Albuterol-free days, %	30.8	24.0	6.9 (-2.3, 16.1)	NS
CI = Confidence interval; NS = Non-significant				

The frequency of adverse events was similar between patients taking *Advair HFA* and FP. The most common adverse events reported (≥5% in the *Advair* arm) were viral ear, nose and throat infections (*Advair* 17%; FP 14%), viral respiratory infections (11% vs. 5%), headache (7% each), upper respiratory inflammation (6% vs. 9%), nasal signs and symptoms (6% vs. 2%), ear, nose and throat infections (5% vs. 9%), and throat and tonsil discomfort and pain (5% each).

Comparison of Advair Diskus Versus Higher Dose FP as Initial Maintenance Therapy

A randomized, double-blind, parallel group study conducted in Norway, Finland and Sweden compared *Advair Diskus* 100/50 with more than double the dose of FP (250 mcg) in patients who were taking only short-acting $beta_2$-agonists, but required further treatment with a controller medication. [26,193] Patients included in this study were 18-60 years of age with at least a 3 month history of reversible airway obstruction. For entry, patients were required to have a positive reversibility test or variability in peak expiratory flow. During a 2-week run-in period, patients who had a cumulative symptom score of ≥7 during the last 10 day period and/or used rescue medication on ≥50% of days were randomized to 12 weeks of treatment with either *Advair Diskus* 100/50 twice daily or FP 250 mcg twice daily via the *Diskus* device. The primary endpoint was change in morning PEF from baseline over weeks 1-12.

A total of 154 patients were randomized to treatment. The patients had a mean age of approximately 37 years, 61% were female, and mean FEV_1 was 90%-91% of predicted across treatment groups at baseline. Additionally, at baseline, patients randomized to FP reported 28% albuterol-free days compared with 23% albuterol-free days in patients randomized to receive *Advair Diskus*. Patients receiving *Advair Diskus* had a significant improvement in morning PEF over weeks 1-12 (Table 45). Additionally, at each week of the 12 treatment weeks, patients receiving *Advair Diskus* 100/50 had a significantly higher adjusted mean change in morning PEF compared with patients receiving FP 250 mcg ($P<0.01$). Similar results were seen with evening PEF. Patients randomized to *Advair Diskus* also showed significant improvements in clinic FEV_1 compared with patients receiving higher dose of FP at each of the three clinic visits ($P\leq0.015$).

Table 45. Adjusted* Mean Change in Morning PEF Over Weeks 1-12

	***Advair Diskus* 100/50 BID** **n=75**	**FP 250 mcg BID** **n=79**
Mean PEF Over Weeks 1-12, L/min	58.6	30.4
Adjusted Mean Treatment Difference (95% CI), L/min	28.2 (15.2-41.1)	
P-Value	<0.0001	
*Adjustment for age, sex, height, and baseline morning PEF		

An asthma control day was defined as a 24-hour period with PEF variability less than 10% and no asthma symptoms or short-acting $beta_2$-agonist use. Both groups demonstrated an improvement in the percent of patients with total asthma control; however, there was no significant difference between treatment groups. Similarly, no difference was seen between groups in the time to first treatment week with acceptable asthma control (defined as a week with daily PEF variability less than 20%, short-acting $beta_2$-agonist use on ≤2 occasions per week and a weekly total symptom score ≤3). There was no significant difference in time to withdrawal between the two treatment groups.

A similar percentage of patients reported adverse events in the two treatment groups. The most frequently reported adverse event was common cold, 32% in the FP group and 24% in the *Advair* group, followed by hoarseness (10% and 8%), headache (4% and 8%), sore throat (5% and 7%), influenza (6% and 5%), sinusitis (5% each) and respiratory tract infection (4% and 5%).

Advair Diskus Compared with Higher Dose FP in Children with Asthma

In a randomized, double-blind, double dummy, parallel group, non-inferiority study in 12 European countries, *Advair Diskus* 100/50 was compared with twice the ICS dose in children with asthma previously receiving medium doses of ICS.[13,14] Children ages 4-11 years were included if they had a clinical history of asthma for ≥6 months and documented airway reversibility of ≥15% based on either FEV_1 or PEF. Patients were required to be receiving medium dose ICS (beclomethasone dipropionate (BDP) hydrofluoroalkane (HFA) non fine particle 400-500 mcg/day or BDP HFA fine particle 200 mcg/day, budesonide 400 mcg/day or FP 200-250 mcg/day) for at least 3 months prior to the screening visit and at a stable dose for at least 4 weeks prior to the screening visit. Patients meeting these criteria entered a 4-week run-in period where they received FP 100 mcg (via the *Diskus* device) twice daily along with a short-acting $beta_2$-agonist as needed. If during the run-in period patients did not achieve the criteria for 'Well Controlled' for two or more weeks, they were randomized to receive treatment with either *Advair Diskus* 100/50 twice daily or FP 200 mcg twice daily (via *Diskus*) for 12 weeks.

The primary endpoint was the change from baseline in mean morning PEF over 12 weeks based on the Intent-to-Treat Population (ITT) and the Per Protocol Population (PP). The PP Population consisted of patients in the ITT Populations who did not have any protocol violations which could impact the treatment effect. *Advair Diskus* was deemed non-inferior if the 95% confidence interval (CI) fell within ±12 L/min for both the ITT and the PP Populations. In the event that the lower confidence limit (2.5% 1-sided significance) exceeded 0, superiority could be established.

For the ITT Population, 150 patients were randomized to treatment with *Advair Diskus* and 153 patients received FP. The PP Population consisted of 129 patients receiving *Advair*and 136 patients receiving FP. The two treatment groups were well matched for all demographic and baseline parameters. For the primary endpoint, mean change in morning PEF, an increase in morning PEF was shown following both treatments

and non-inferiority of *Advair* to FP was demonstrated. Over weeks 1-12, improvement in morning PEF was significantly greater with *Advair* compared with FP in the ITT Population (adjusted mean change FP = 19.3 L/min, *Advair* = 26.9 L/min; treatment difference = 7.6, 95% CI: 1.7, 13.5; *P* = 0.012). Similar findings were seen in the PP Population (adjusted mean change FP = 18.4 L/min, *Advair* = 27.7 L/min; treatment difference = 9.3, 95% CI: 3.2, 15.3; *P* = 0.003).

The proportion of patients achieving 'Totally Controlled' and 'Well Controlled' asthma, based on predefined criteria from the **G**aining **O**ptimal **A**sthma Contro**L** (GOAL) study,[10] were evaluated as secondary endpoints. The proportion of patients achieving the eight week definition of 'Totally Controlled' and 'Well Controlled' asthma, based on treatment weeks 5-12, were similar between treatment groups.

Both treatments were well tolerated with the incidence of adverse events being similar in both groups. The most frequently reported adverse (≥5%) events were headache (*Advair* 18% vs. FP 15%), nasopharyngitis (9% vs. 12%), rhinitis (8% vs. 7%), cough (5% vs. 7%), allergic rhinitis (4% vs. 7%), abdominal pain (5% vs. 4%), and influenza (2% vs. 5%).

7.4 Comparison with Montelukast in Asthma

Comparative Studies with Montelukast

Study 1

A 12-week, randomized, double-blind, multicenter study was conducted in 423 patients with asthma (FEV_1 50-80% of their predicted normal value) who were symptomatic on short-acting beta-agonists alone.[27,28] Following an 8 to 14 day screening period, patients who remained symptomatic were randomized to treatment with *Advair Diskus* 100/50 twice daily, or montelukast 10 mg once a day. Patients were considered to be symptomatic if they required rescue albuterol on more than 5 days during the 7 days that preceded randomization, or had a diary card symptom score of ≥2 on 3 or more days for chest tightness, wheezing, or shortness of breath. Baseline demographics are shown in Table 46.

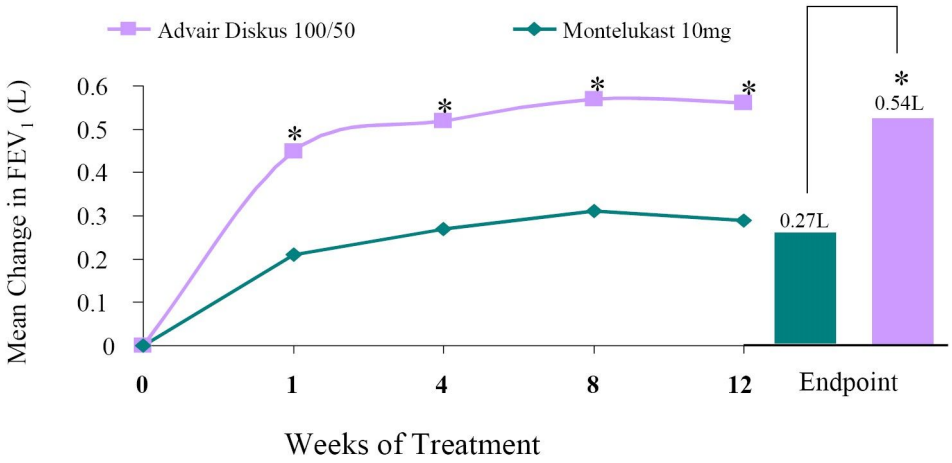
Table 46. Baseline Demographics

	***Advair Diskus* 100/50**	**Montelukast 10 mg**
Mean Age (years)	36.5	35.8
Female (%)	50	49
Mean Pre-dose FEV_1 (L)	2.46	2.40
Mean FEV_1 (% predicted)	67.8	66.4
Mean AM PEF (L/min)	383.0	365.6

The primary efficacy outcome was change from baseline in morning pre-dose FEV_1 at endpoint. This measurement was taken prior to the morning dose of *Advair Diskus*, and approximately 12 hours following the dose of montelukast, which was administered in the evening. Patients treated with *Advair Diskus* 100/50 experienced significantly greater improvements in FEV_1 than did patients treated with montelukast 10 mg daily.

The improvements in FEV_1 represented a 23% increase from baseline in patients treated with *Advair Diskus* 100/50 and an 11% increase from baseline in patients treated with montelukast 10 mg. These results are shown in Figure 22 below.

Figure 22. Change from Baseline in Morning Pre-dose FEV_1



Baseline AM predose FEV_1 was 2.46L and 2.40L for Advair Diskus and montelukast groups, respectively.
* p<0.001 vs montelukast

Secondary and other endpoints were also analyzed. Compared with montelukast, treatment with *Advair Diskus* resulted in significant improvements in forced expiratory flow rate at 25% to 75% (FEF_{25-75}), morning peak expiratory flow (AM PEF), evening PEF (PM PEF), the number of symptom-free days, daytime asthma symptom scores (shortness of breath, wheeze, chest tightness), the percent of nights with no awakenings, and the percent of rescue-free days (Table 47).

Table 47. Secondary and Other Endpoints (Change from Baseline at Endpoint)

Efficacy Parameter	*Advair Diskus* 100/50	Montelukast 10 mg	*P*-value
FEF_{25-75}	0.8 L/s	0.3 L/s	≤0.001
AM PEF	89.9 L/min	34.2 L/min	≤0.001
PM PEF	69.9 L/min	31.1 L/min	≤0.001
Percent of symptom-free days	48.9	21.7	≤0.001
Daytime asthma symptom score	-1.0	-0.6	≤0.001
Percent of nights with no awakenings	23.0	15.5	≤0.001
Percent of rescue-free days	53.0	26.2	≤0.001
Baseline FEF_{25-75} was 1.72 and 1.65 L/s for *Advair Diskus* and montelukast groups, respectively. Baseline AM PEF was 383 and 365.6 L/min for *Advair Diskus* and montelukast groups, respectively. Baseline PM PEF was 417.9 and 396.7 L/min for *Advair Diskus* and montelukast groups, respectively. Baseline percent of symptom-free days was 3.9% and 5.8% for *Advair Diskus* and montelukast groups, respectively. Baseline daytime symptom score was 1.6 for both *Advair Diskus* and montelukast groups. Baseline percent of nights with no awakenings was 66.7 and 62.4 for *Advair Diskus* and montelukast groups, respectively. Baseline percent of rescue-free days was 5.9 and 6.8 for *Advair Diskus* and montelukast groups, respectively.			

Additionally, there was a significant difference in asthma exacerbations between the groups treated with *Advair Diskus* 100/50 and montelukast 10 mg. Fewer patients treated with *Advair Diskus* 100/50 (n=0) experienced an asthma exacerbation compared with those treated with montelukast 10 mg (n=11, 5%; $P < 0.001$).

There was a significant difference in patient satisfaction scores, in favor of treatment with *Advair Diskus* 100/50 compared with montelukast 10 mg. Significantly more patients receiving *Advair Diskus* 100/50 reported that they were satisfied or very satisfied with the study medication compared with those patients receiving montelukast 10 mg (81% versus 58%; $P < 0.001$). Additionally, compared with montelukast 10 mg, significantly more patients treated with *Advair Diskus* 100/50 were satisfied or very satisfied with how well the study medication worked (83% versus 59%, $P < 0.001$).

Onset of effect

The onset of effect was evaluated by comparing changes from baseline in efficacy parameters over the first 14 days of therapy.[28] Treatment with *Advair Diskus* 100/50 resulted in significantly greater improvements ($P < 0.001$) in efficacy parameters on Day 1 compared with montelukast 10 mg (Table 48). In addition, significantly greater improvements in efficacy parameters were maintained on Day 14 and were continued throughout the study.

Table 48. Change in Efficacy Parameter After 1 and 14 Days

	Day 1		Day 14	
	***Advair Diskus* 100/50**	**Montelukast 10 mg**	***Advair Diskus* 100/50**	**Montelukast 10 mg**
AM PEF (L/min)	+43.7*	10	+67.3*	29.5
Albuterol Use (puffs/day)	-2.2*	-1.3	-2.9*	-1.6
Symptom Score (% change)	-33.4*	-8.1	-52.8*	-22.1
*$P<0.001$ versus Montelukast 10 mg				

Efficacy based upon baseline asthma severity

In a subset analysis, efficacy measures (FEV_1, AM PEF, symptoms, and rescue albuterol use) and patient preference measures were evaluated in patients with baseline FEV_1 values of 50-70% or >70-80% of predicted normal. [27] Regardless of baseline asthma severity, *Advair Diskus* resulted in significantly greater improvements in overall asthma control and was preferred by significantly more patients compared with montelukast.

Study 2

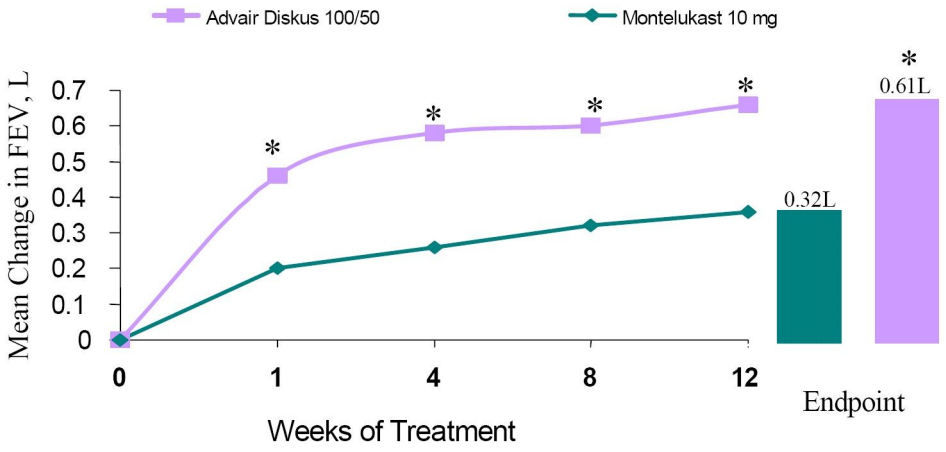
A separate study with an identical design revealed similar results in comparing *Advair Diskus* 100/50 with montelukast 10 mg. [194,195] In this study, 432 patients with asthma (baseline FEV_1 was 50-80% of predicted) who were symptomatic on short-acting beta-agonists alone were randomized to receive either *Advair Diskus* 100/50 twice daily or montelukast 10 mg once a day. Baseline demographics are shown in Table 49.

Table 49. Baseline Demographics

	***Advair Diskus* 100/50**	**Montelukast 10 mg**
Mean Age (years)	34.8	36
Female (%)	54	55
Mean Pre-dose FEV_1 (L)	2.42	2.39
Mean FEV_1 (% predicted)	67.0	66.6
Mean AM PEF (L/min)	361.9	361.7

In this study, *Advair Diskus* was shown to be superior to montelukast in improving AM pre-dose FEV_1 (Figure 23). Similar to the previous study, this measurement was taken prior to the morning dose of *Advair Diskus* 100/50 and approximately 12 hour after the dose of montelukast 10 mg, which was administered in the evening.

Figure 23. Change from Baseline in Morning Pre-dose FEV_1



Baseline AM predose FEV_1 was 2.42L and 2.39L for Advair and montelukast groups, respectively.
* p<0.001 vs montelukast

Secondary and other endpoints were also analyzed. Compared with montelukast, treatment with *Advair Diskus* resulted in significant improvements in forced expiratory flow rate at 25% to 75% (FEF_{25-75}), AM PEF, evening PEF, the number of symptom-free days, daytime asthma symptom scores (shortness of breath, wheeze, chest tightness), the percent of nights with no awakenings, and the percent of rescue-free days (Table 50).

Table 50. Secondary and Other Endpoints (Change from Baseline at Endpoint)

Efficacy Parameter	*Advair Diskus* 100/50	Montelukast 10 mg	*P*-value
AM PEF	81.4 L/min	41.9 L/min	≤0.001
PM PEF	64.6 L/min	38.8 L/min	≤0.001
Percent of symptom-free days	40.3	27.0	≤0.001
Combined asthma symptom score	-1.0	-0.7	≤0.001
Percent of nights with no awakenings	29.8	19.6	≤0.011
Percent of rescue-free days	53.4	26.7	≤0.001
Baseline AM PEF was 361.9 and 361.7 L/min for *Advair Diskus* and montelukast groups, respectively. Baseline PM PEF was 395.3 and 398.7 L/min for *Advair Diskus* and montelukast groups, respectively. Baseline percent of symptom-free days was 7.9% and 5.8% for *Advair Diskus* and montelukast groups, respectively. Baseline combined symptom score was 1.6 and 1.5 for *Advair Diskus* and montelukast groups, respectively. Baseline percent of nights with no awakenings was 59.9% and 60.2% for *Advair Diskus* and montelukast groups, respectively. Baseline percent of rescue-free days was 8.6% and 8.4% for *Advair Diskus* and montelukast groups, respectively.			

There were a small number of asthma exacerbations in both treatment groups during the study period. Six patients (3%) treated with *Advair Diskus* 100/50 had an exacerbation, compared with 13 patients (6%) treated with montelukast 10 mg. The difference between groups was not significant ($P = 0.109$).

There was a significant difference in patient satisfaction scores in favor of treatment with *Advair Diskus* 100/50 compared with montelukast 10 mg. Significantly more patients receiving *Advair Diskus* reported that they were satisfied with the study medication compared with those patients receiving montelukast 10 mg (83% versus 63%; $P < 0.001$). Significantly more ($P < 0.001$) patients treated with *Advair Diskus* were also satisfied with how fast and how long their medication worked compared with montelukast. Additionally, significantly more patients treated with *Advair Diskus* reported that they would use their study medication again and would ask their physician for a prescription (58% versus 32%; $P < 0.001$).

Efficacy based upon baseline asthma severity

Lung function was also assessed in a subset of patients stratified based upon baseline severity of airway obstruction (FEV_1 50 - 70 and FEV_1 > 70). Patients treated with *Advair Diskus* 100/50 demonstrated a superior increase in mean change from baseline in morning PEF baseline, regardless of asthma severity, compared to montelukast ($P \leq 0.001$).

In addition, patients treated with *Advair Diskus* 100/50 demonstrated a superior increase in percent change in FEV_1 from baseline regardless of asthma severity ($P < 0.001$, see Table 51).

Table 51. FEV_1 Responder Analysis

	***Advair Diskus* 100/50**	**Montelukast 10 mg**
Change in FEV_1 (L)	0.61*	0.32
Percent change in FEV_1	27*	13
Patients with ≥12% increase in FEV_1	74%*	46%
Patients with ≤0% change in FEV_1	3%*	22%
*$P < 0.001$ versus montelukast		

7.5 Comparison with Montelukast in Children with Asthma

In a randomized, double-blind, double-dummy, parallel-group study, the efficacy and safety of *Advair Diskus* was compared with montelukast in children aged 6 to 14 with persistent asthma.[30] A total of 548 children with a forced expiratory volume in 1 second (FEV_1) of 55% - 80% predicted who were symptomatic on a short-acting $beta_2$-agonist were randomized to receive *Advair Diskus* 100/50 twice daily (n=281) or montelukast 5 mg once daily (n=267) for 12 weeks. The primary endpoint was mean change from baseline in morning peak expiratory flow (PEF) over weeks 1-12. Other endpoints included additional measures of lung function, asthma symptoms, rescue medication use, and asthma control.

Baseline demographics and disease characteristics were similar between the treatment groups with the exception of a higher percentage of males in the montelukast group (67%) compared with the *Advair Diskus* group (56%). Mean age was 9.3 years, and mean baseline FEV_1 was 72.9% percent predicted in both treatment groups. For the primary endpoint, there was a greater mean change from baseline in morning PEF in the *Advair* group (45.8 L/min) compared with the montelukast group (28.7 L/min) resulting in satistically significant treatment difference of 17.16 L/min (P<0.001). Similar improvements in FEV_1 and evening PEF were observed (Table 52).

Table 52. Improvements in Lung Function

Endpoint	***Advair Diskus* 100/50**	**Montelukast 5 mg**	**Treatment Difference (95% CI) *P*-Value**
Adjusted Mean Change from Baseline in Morning PEF Over Weeks 1-12 (L/min)	45.8	28.7	17.16 (9.23-25.08) *P*<0.001
Adjusted Mean Change from Baseline in FEV_1 at Week 12 (L)	0.47	0.30	0.16 (0.11-0.21) *P*<0.001
Adjusted Mean Change from Baseline in Evening PEF Over Weeks 1-12 (L/min)	46.2	28.0	18.35 (10.35-26.35) *P*<0.001

Patients receiving *Advair* compared with montelukast were significantly more likely to have symptom-free days (odds ratio 1.74; P=0.025) and rescue-free days (odds ratio 3.24; P<0.001).. No significant difference was seen in the percentage of nights with no awakenings. In addition, patients in the *Advair Diskus* group had significantly more well-controlled asthma weeks, as defined in the Gaining Optimal Asthma controL (GOAL) study compared with patients receiving montelukast. The median percentage of well-controlled

asthma weeks was 83.3% in the *Advair* group and 66.7% in the montelukast group over the entire treatment period, resulting in a treatment difference of 16.7% ($P<0.001$).

Health-related quality of life was measured using the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) for the children and Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) for the caregiver. A clinically meaningful change for both questionnaires has been previously determined to be ≥0.5. For both treatments, a clinically meaningful change from baseline was observed with both questionnaires. There was no statistically significant difference between the treatment groups in the mean change from baseline in the PAQLQ score. However, there was a significant difference in the mean change from baseline in the PACQLQ score in favor of *Advair* (1.5) compared with montelukast (1.0) resulting in a treatment difference of 0.54 ($P=0.028$).

Adverse events were similar between treatment groups. Headache was the most frequently reported adverse event in each treatment group (*Advair* 23%; montelukast 27%). Exacerbations were defined as ≥ 1 of the following: worsening of asthma that required an emergency room visit or hospitalization; an unscheduled doctor visit or contact requiring treatment with oral, parenteral or inhaled corticosteroids, or treatment with nebulized albuterol; the use of ≥ 12 puffs of albuterol in a 24 hour period; or the use of ≥ 10 puffs of albuterol on each of 2 consecutive days. More patients in the montelukast (23.2%) group had at least 1 exacerbation during the study period compared with *Advair* (10.3%). There were three asthma exacerbations requiring hospitalization in the montelukast group (one occurring the day after the end of study treatment) and none in the *Advair* group. In a *post-hoc* analysis, the mean rate of exacerbations over 12 weeks was 0.12 in the *Advair* group compared with 0.30 in the montelukast group (*Advair*/montelukast ratio 0.40; $P<0.001$).

7.6 Comparison with Fluticasone Propionate plus Montelukast in Asthma

Comparative Studies

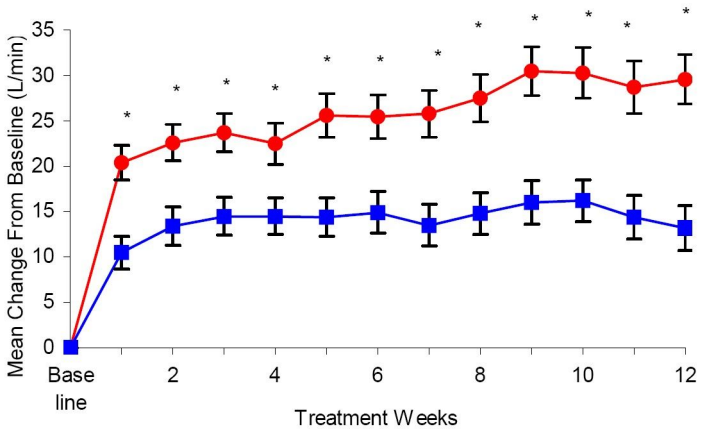
Study 1

A randomized, double-blind, double-dummy, parallel-group study compared the efficacy and safety of *Advair Diskus* with the addition of montelukast to existing treatment with FP. [31] A total of 447 patients with asthma (forced expiratory volume in one second [FEV_1]=50-80% of predicted) previously treated with a low to moderate dose of inhaled corticosteroids (beclomethasone dipropionate 252-420 mcg/day, budesonide 400 mcg/day, flunisolide 1000 mcg/day, FP 176-220 mcg/day, or triamcinolone acetonide 600-800 mcg/day) participated in the study. During a three-week run-in period, all patients received FP 100 mcg twice daily via Diskus. Patients who remained symptomatic were then randomized to treatment with *Advair Diskus* 100/50 or montelukast 10 mg once daily plus FP 100 mcg twice daily via Diskus for 12 weeks.

Throughout the study, patients recorded morning and evening peak expiratory flow (PEF), rescue albuterol use, and daytime symptom scores for chest tightness, wheezing, and shortness of breath. In addition, pulmonary function was assessed after 1, 4, 8, and 12 weeks of therapy. The incidence of exacerbations, defined as the requirement for asthma medications other than those permitted by the protocol (i.e., oral or parenteral corticosteroids), was also assessed.

Overall mean morning PEF was significantly improved in the *Advair Diskus* group (24.9 L/min) compared with the montelukast plus FP group (13.0 L/min, $P < 0.001$) as illustrated in Figure 24.

Figure 24. Improvement in Morning PEF with *Advair Diskus* vs. FP plus Montelukast over 12 Weeks



*$P \leq 0.011$ vs FP+ Montelukast

Mean morning PEF was significantly improved in the *Advair Diskus* group compared with the montelukast plus FP group within the first day of treatment and was maintained throughout the entire 12-week treatment period. Evening PEF followed a similar pattern. *Advair Diskus* also resulted in significantly greater improvements in FEV_1 compared with the montelukast plus FP group (0.34 L versus 0.20 L, $P \leq 0.001$). The improvement in FEV_1 observed after treatment with *Advair Diskus* (15%) was almost double the improvement observed after treatment with montelukast plus FP (8%). Patients treated with *Advair Diskus* had a significant reduction in rescue albuterol use compared with the group treated with montelukast plus FP ($P < 0.001$), and the percentage of albuterol-free days was significantly higher during treatment with *Advair Diskus* compared with montelukast plus FP ($P = 0.032$) (Table 53). The mean shortness of breath symptoms scores were also significantly improved after *Advair Diskus* compared with montelukast plus FP ($P = 0.017$).

Table 53. Secondary Endpoints: Change From Baseline Over Weeks 1-12

	***Advair Diskus* 100/50**	**FP 100 mcg + montelukast**	**P-value**
Rescue-free days (%)	26.3	19.1	0.032
PM PEF (L/min)	18.9	9.6	<0.001
Daytime chest tightness symptom score	-0.49	-0.43	0.521
Daytime shortness of breath symptom score	-0.56	-0.4	0.017
Daytime wheeze symptom score	-0.41	-0.38	0.279

Significantly fewer patients treated with *Advair Diskus* [4 (2%)] experienced an exacerbation compared with montelukast plus FP [13 (6%)] ($P = 0.031$). Both treatments were well tolerated. The most commonly reported drug-related adverse events in the *Advair Diskus* and montelukast plus FP groups, respectively, included oral candidiasis (1%, 2%), sore throat (1%, 3%), hoarseness (2%, <1%), and headache (2%, 1%).

Study 2

In a second, similarly designed study, Ringdal et al compared the efficacy and safety of *Advair Diskus* 100/50 versus the addition of montelukast to existing treatment with FP. [32] A total of 725 patients with asthma (baseline FEV_1=74-76% of predicted) previously treated with inhaled corticosteroids (beclomethasone dipropionate, budesonide, or flunisolide 400-1000 mcg/day, or FP 200-500 mcg/day) participated in the study. During a four-week run-in period, all patients received FP 100 mcg twice daily via Diskus. Patients who remained symptomatic were then randomized to treatment with *Advair Diskus* 100/50 or montelukast 10 mg once daily plus FP 100 mcg twice daily via Diskus for 12 weeks. Throughout

the study, patients recorded morning and evening PEF, symptoms, and use of rescue medication. Pulmonary function (FEV_1) was assessed after 4, 8, and 12 weeks of therapy. The incidence and severity of exacerbations were also collected. Exacerbations were classified as mild (a deterioration in asthma requiring a clinically relevant increase in albuterol use defined as more than three additional inhalations per 24-hour period relative to baseline for more than two consecutive days), moderate (requiring oral corticosteroids and/or antibiotics) or severe (requiring a hospitalization). In addition, patients rated their satisfaction with treatment at the beginning and end of the study.

The primary efficacy endpoint, mean morning PEF, was significantly higher with *Advair Diskus* 100/50 compared with montelukast plus FP throughout the study. The adjusted mean improvement from baseline in morning PEF was 36 and 19 L/min for *Advair Diskus* 100/50 and montelukast plus FP, respectively ($P < 0.05$). Mean evening PEF followed a similar pattern. Treatment with *Advair Diskus* 100/50 also resulted in significantly greater improvements in FEV_1 ($P < 0.05$) and the percentage of symptom-free days and nights ($P < 0.05$) compared with montelukast plus FP. Additionally, a significantly greater percentage of patients treated with *Advair Diskus* 100/50 (93%) were satisfied or very satisfied with treatment compared with montelukast plus FP (84%) ($P < 0.05$). Improvements from baseline in secondary endpoints are illustrated below in Table 54:

Table 54. Secondary Endpoints at Baseline and Over Weeks 1-12

	***Advair Diskus* 100/50**		**FP 100 mcg + montelukast**		**P-value**
	Baseline	**Weeks 1-12**	**Baseline**	**Weeks 1-12**	
Mean PM PEF (L/min)	385.7 ± 5.3	416.5 ± 2.2	380.3 ± 4.9	395.5 ± 2.1	0.0001
FEV_1 (L)	2.47 ± 0.04	2.73 ± 0.03	2.41 ± 0.04	2.58 ± 0.03	0.0001
Median % symptom-free days	7.1	50	7	38.5	0.017
Median % symptom-free nights	32.1	78.6	30.3	71.4	0.033
Median % rescue-free days	23.5	71.4	20.7	66.7	0.03
Median % rescue-free nights	53.6	92.9	56.7	85.7	NS
NS=not significant					

Significantly fewer patients treated with *Advair Diskus* 100/50 [34 (9.6%)] experienced at least one exacerbation compared with montelukast plus FP [54 (14.6%)] ($P < 0.05$). The time to the first exacerbation was significantly longer in the group treated with *Advair Diskus* 100/50 compared with montelukast plus FP. Both treatments were well tolerated with a similar incidence of adverse events.

7.7 Comparison with Ipratropium-Albuterol in COPD

Comparative Studies

The efficacy and safety of *Advair Diskus* 250/50 twice daily in the treatment of chronic obstructive pulmonary disease (COPD) was compared with that of ipratropium/albuterol via pressurized metered dose inhaler (pMDI) 2 puffs four times (36 mcg/206 mcg) a day in two identical, multicenter, randomized, double-blind, double-dummy, parallel-group studies. In study 1, [51,196] 365 patients were included, and study 2 [52,197] included 361 patients. Patients enrolled in these studies had a diagnosis of COPD with or without symptoms of chronic bronchitis. In the two studies, a total of 56% of patients (n=409) were identified by the study investigators as having COPD associated with chronic bronchitis symptoms (with or without emphysema), while 44% (n=315) were identified as having COPD associated with emphysema alone.

Patients were 40 years of age and older with a current or prior cigarette smoking history of at least 10 pack-years, and with a diagnosis of COPD as defined by the American Thoracic Society (ATS).[198] Patients were symptomatic and had used a short-acting inhaled bronchodilator as needed or on a scheduled bases for at least 30 days. Patients were required to have airflow obstruction as demonstrated by a FEV_1/FVC ratio of ≤70%. Patients were also required to have an FEV_1 greater than 0.70 L and ≤70% of predicted or an FEV_1 less than 0.70 L and 40%-70% of predicted.

During an 8 to 14 day run-in period, patients replaced previous bronchodilators with albuterol via pMDI or nebulizer (using unit-dose nebules) given on an as-needed basis. During the run-in and treatment phases, all concurrent use of respiratory medications (except for antihistamines, nasal decongestants, and other intranasal medications for the treatment of rhinitis) were discontinued. Patients were randomized

to treatment with *Advair Diskus* 250/50 twice daily or ipratropium/albuterol 2 puffs four times a day for 8 weeks.

The primary efficacy outcome was mean change from baseline to Endpoint in morning pre-dose FEV_1. Secondary outcomes of efficacy were the morning PEF, FEV_1 AUC_6, percent symptom-free nights, TDI score, and overall daytime symptom score. Related secondary outcomes were the percent albuterol rescue-free days, percent albuterol rescue-free nights, nighttime awakenings secondary to lung/respiratory symptoms and sleep symptom score.

Results

Baseline patient demographics and lung function were similar among the treatment groups (Table 55).

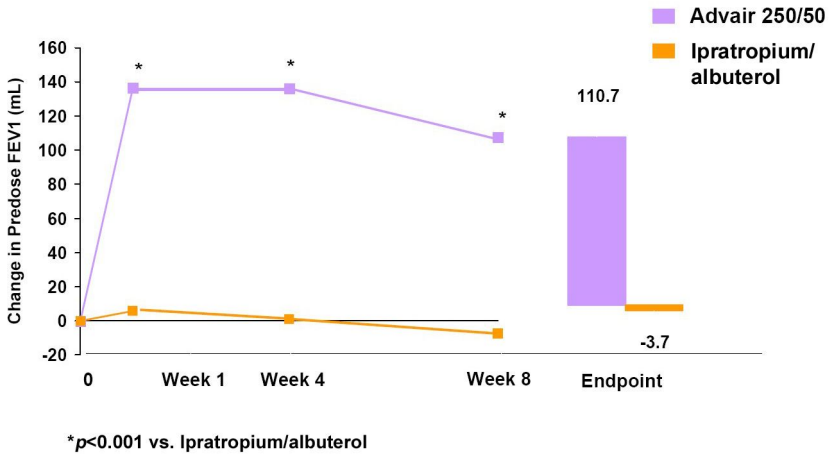
Table 55. Baseline Characteristics and Lung Function

	Study 1 [196]		Study 2 [197]	
	Advair Diskus 250/50	Ipratropium/ albuterol	*Advair Diskus* 250/50	Ipratropium/ albuterol
	n=182	n=183	n=180	n=181
Mean age (years)	63.3	63.9	63.7	65.4
Caucasian (%)	96	95	82	91
Male (%)	59	60	64	62
Current smokers (%)	50	49	49	48
Mean smoking history (pack-years)	61.7	61.2	57.5	59.8
Mean baseline FEV_1 (L, pre-dose)	1.34	1.3	1.31	1.2
Mean baseline FEV_1, % predicted	44.1	43.2	43.7	41.6
Mean FEV_1, % reversible	16.8	15.5	18.2	19.4
Mean FEV_1/FVC (pre-dose)	0.52	0.52	0.52	0.5
FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; L = liters				

Primary Efficacy Outcome: Morning Pre-dose FEV_1

In both studies,[196,197] improvement in morning pre-dose FEV_1 in patients who received *Advair Diskus* 250/50 was significantly greater than in those who received ipratropium/albuterol. In Study 1 at Endpoint (see Figure 25 below), [51,196] AM pre-dose FEV_1 increased by 110.7 mL in the patients receiving *Advair Diskus* as compared with a decrease of 3.7 mL for those receiving ipratropium/albuterol (P<0.001). In Study 2 at Endpoint , [52,197] AM pre-dose FEV_1 increased by 124.0 mL in the *Advair Diskus* group as compared with a decrease of 3.2 mL for the ipratropium/albuterol group (P<0.001).

Figure 25. Change from Baseline in Pre-dose Morning FEV_1 [196]



*p<0.001 vs. Ipratropium/albuterol

Secondary Efficacy Outcomes

In Study 1, [51,196] patients who received *Advair Diskus* experienced significantly greater improvements from baseline than those in the ipratropium/albuterol group for all secondary outcomes. Most related secondary outcomes were also significantly improved in patients receiving *Advair Diskus*. At Endpoint, significantly greater improvements in AM PEF, FEV_1 AUC_6 (See Figure 26 below), percent of symptom-free nights, dyspnea as measured by TDI score, and overall daytime symptom score were observed in the *Advair Diskus* group as compared with ipratropium/albuterol ($P \leq 0.011$). Statistically significant improvements were observed in the *Advair Diskus* group compared to the ipratropium/albuterol group for all related secondary outcomes except percent rescue-free days.

In Study 2, [52,197] patients who received *Advair Diskus* experienced significantly greater improvements from baseline than those in the ipratropium/albuterol group for AM PEF, FEV_1 AUC_6, and mean TDI scores. Non-significant differences in changes from baseline were observed in percent symptom-free nights and overall daytime symptom scores as well as all related secondary outcomes in the *Advair Diskus* group compared to the ipratropium/albuterol group. See Table 56.

Table 56. Mean Change from Baseline at Endpoint in Secondary Outcomes and Related Secondary Outcomes

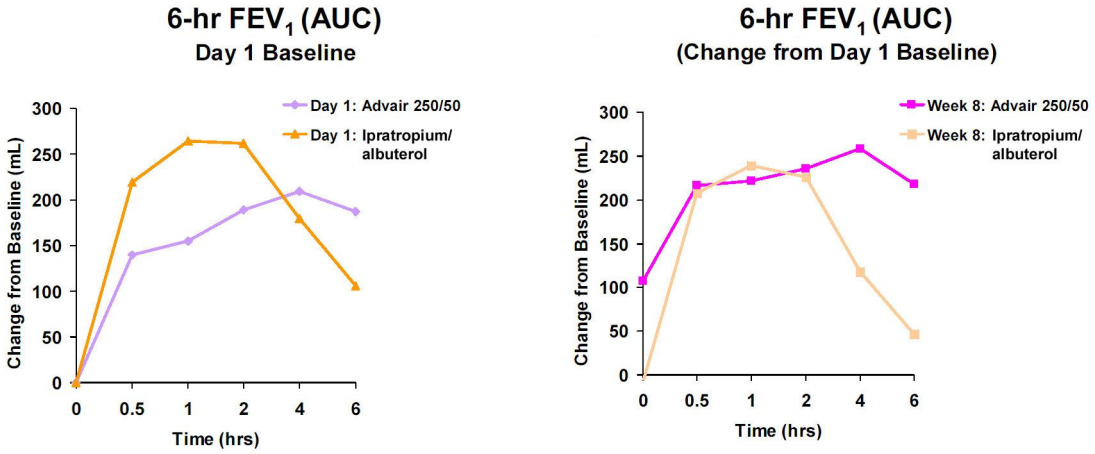
	Study 1[196]		**Study 2[197]**	
	Advair Diskus 250/50 n=182	Ipratropium/ albuterol n=183	*Advair Diskus* 250/50 n=180	Ipratropium/ albuterol n=181
SECONDARY OUTCOMES				
AM PEF (L/min)	37.0*	7.0	35.9*	3.8
FEV_1 AUC_6 (L-hr)	1.39*	0.90	1.39†	0.98
symptom-free nights (%)	28.4*	7.7	20.5	9.7
TDI score§	2.7*	1.2	2.7†	1.5
Overall daytime symptom score	-48.5†	-29.8	-52.5	-36.3
RELATED SECONDARY OUTCOMES				
Rescue-free days (%)	37.6	27.7	34.5	25.7
Rescue-free nights (%)	22.4†	8.7	17.8	5.7
Nighttime awakenings (awake/night)	-0.58*	-0.2	-0.39	-0.15
Sleep symptom score	-11.8†	-4.5	-12.7	-7.4

*$P<0.001$, †$P \leq 0.011$

§Difference in TDI scores between *Advair Diskus* and ipratropium/albuterol was >1 unit, indicating a clinically meaningful change [199]

AM=morning; AUC_6=6-hour area-under-the-curve; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; hr=hour; L=liters; PEF=peak expiratory flow; TDI=Transition Dyspnea Index

Figure 26. Serial FEV_1 at Week 8: Mean Change from Baseline[196]



Safety

The rate of adverse events that occurred in at least 3% of patients is shown in Table 57 below. Overall, the adverse events reported occurred with a similar frequency between groups. In Study 1, a total of 39% of patients in the *Advair Diskus* group reported at least one adverse event, compared with 42% of those in the ipratropium/albuterol group. In Study 2, a total of 45% of patients in the *Advair Diskus* group reported at least one adverse event, compared with 47% of those in the ipratropium/albuterol group.

Table 57. Adverse Events (%) Occurring in at Least 3% of Patients in Either Study

	***Advair Diskus* 250/50**	**Ipratropium/ albuterol**	***Advair Diskus* 250/50**	**Ipratropium/ albuterol**
	Study 1[196]		**Study 2[197]**	
Headaches	4	6	9	7
Common Cold	3	1	6	3
Sore Throat	3	4	3	4
Nausea	<1	1	3	3
Cough	2	2	2	4
Xerostomia	2	0	2	3
Diarrhea	2	2	3	2
Upper respiratory tract infection	2	4	<1	<1
Back Pain	2	4	2	1
Candida	3	0	<1	<1

In Study 1,[196] 6% and 5% of patients reported an exacerbation of COPD in the *Advair Diskus* and ipratropium/albuterol groups, respectively. In Study 2,[197] 3% and 8% of patients reported an exacerbation of COPD in the *Advair Diskus* and ipratropium/albuterol groups, respectively. Respiratory infection was reported as the primary cause for the majority (≥50%) of exacerbations.

7.8 Comparison with Tiotropium in COPD

The Inspire Study - Advair Diskus 500/50 Two-Year Study

A 2-year, randomized, double-blind, double-dummy study compared *Advair Diskus* with tiotropium on the rate of exacerbations in patients with severe COPD.[50,200] Patients were included in this study if they were 40-80 years of age with severe COPD (as defined by GOLD guidelines), had a history of COPD exacerbations (but not within 6 weeks prior to the study), a post-bronchodilator forced expiratory volume in one second (FEV_1) less than 50% of predicted, a post-bronchodilator FEV_1/forced vital capacity (FVC) ratio ≤70%, a minimum score of ≥ 2 on the Modified Medical Research Council Dyspnea Scale, poor reversibility of airflow obstruction (defined as ≤ 10% increase in predicted FEV_1), and a smoking history of ≥ 10 pack-years. Patients who had a medical diagnosis of asthma, had undergone lung transplantation

or lung volume reduction surgery, or who required oxygen therapy for more than 12 hours per day were excluded.

Patients meeting inclusion criteria entered a 2-week run-in phase where they discontinued their COPD medications and were given prednisolone 30 mg/day and salmeterol 50 mcg twice daily. After which, patients were randomized to *Advair Diskus* 500/50 twice daily plus placebo via HandiHaler or tiotropium 18 mcg once daily via HandiHaler plus placebo via *Diskus* for 104 weeks of treatment. All patients received albuterol to use as needed during the run-in and treatment periods.

The primary endpoint for the study was the rate of healthcare utilization (HCU) COPD exacerbations which was defined as all exacerbations that required the use of oral corticosteroids, antibiotics or required hospitalization.

A total of 1,323 patients were randomized to treatment. As shown in Table 58, baseline demographics and characteristics were similar between treatment groups. Following randomization, 42% of patients were withdrawn from the tiotropium group and 35% of patients were withdrawn from the *Advair* group. This represents a 29% increase in the probability of withdrawal for the tiotropium group compared with the *Advair* group at any time during the study.

Table 58. Patient Demographics and Baseline Characteristics[50,200]

Parameter	*Advair Diskus* 500/50 (n=658)	Tiotropium 18 mcg (n=665)
Mean age (years)	64.3	64.5
Male (%)	81%	84%
Patients with ≥1 exacerbation in last 12 months (%)	85%	88%
Mean post-bronchodilator FEV_1 % predicted normal	39%	39%

Primary Endpoint

As shown in Table 59, below there was no significant difference between treatments in the rate of HCU COPD-related exacerbations. The higher incidence of withdrawal in the tiotropium group (42%) compared with the group receiving *Advair* (35%) may have underestimated the true rate of exacerbations in the tiotropium group using the negative binomial model.

Table 59. Results of the Primary Endpoint[50,200]

	Advair Diskus 500/50	Tiotropium 18 mcg
Overall rate of exacerbation (using the negative binomial model)	1.28	1.32
Ratio of exacerbation rates (95% CI)	0.967 (0.836 to 1.119)	
P-value	0.656	

Secondary Endpoints

The group receiving *Advair* had a 19% reduction in rate of patients experiencing an exacerbation requiring treatment with oral corticosteroids compared with the group receiving tiotropium with a ratio of rates 0.814 [(95% CI: 0.67 to 0.99); $P = 0.039$]. The ratio of rates for exacerbations requiring antibiotics was 1.186 [(95% CI 1.019 to 1.381); $P = 0.028$] favoring tiotropium.

Results of other secondary endpoints including time to first HCU exacerbation, time to next HCU exacerbation, time to each HCU exacerbation, and duration of each HCU exacerbation showed no statistically significant differences between treatment groups.

Similarly, symptom-defined exacerbations showed no statistically significant difference between treatment groups with respect to rate and duration of symptom-defined exacerbations and time to first, next and each symptom-defined exacerbation. A symptom-defined exacerbation of COPD was defined as an acute worsening of: two or more of the following major symptoms: dyspnea, sputum volume, or sputum purulence; or any one major symptom together with any one of the following minor symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, increased cough or wheeze experienced for at least 2 consecutive days.

The time to withdrawal for any cause was significantly less among patients randomized to *Advair* compared with tiotropium. Cox proportional hazards analysis showed a statistically significant 29% increase in the risk of withdrawal [HR 0.776 (95% CI 0.651 to 0.926); $P = 0.005$].

Post-dose FEV_1 (2 hours after dosing) showed a maximal numerical difference between treatments favoring tiotropium of 0.06 L at week 56 and declined thereafter. No statistically significant difference were observed between treatment groups for this outcome at the end of the study.

Mortality

Mortality was assessed as an other efficacy endpoint. There were 59 deaths during the study (38 randomized to tiotropium and 21 randomized to *Advair*). One death in a patient receiving *Advair* was considered possibly related to treatment. *Advair Diskus* reduced this risk of dying on-therapy at any time within 2 years by 52% [HR 0.476 (95% CI 0.267 to 0.848); $P = 0.012$] compared with tiotropium.

Health Outcomes

Quality of life/health outcome was assessed using the St. George's Respiratory Questionnaire (SGRQ). The SGRQ was administered every 6 months and when patients withdrew from the study. A decrease in score is an indication of an improvement in health status, and a change of at least 4 units is considered clinically significant. The SGRQ score was significantly lower (better) in the *Advair Diskus* group than in the tiotropium group at each time point, although this difference did not reach the minimum clinically important difference. At the end of the study, the adjusted mean treatment difference between groups was -2.1 units (P=0.038). The proportion of patients who achieved a clinically significant improvement in SGRQ score at the end of the study was greater in the *Advair Diskus* group (32%) than in the tiotropium group (27%) [Odds Ratio 1.29; $P = 0.021$].

Safety

The most frequently reported adverse event in each group was COPD exacerbation which occurred in 19% of patients on *Advair* and 16% of patients on tiotropium. Pneumonia was reported more frequently among patients receiving *Advair* (7%) compared with patients receiving tiotropium (3%). Changes in vital signs and ECG abnormalities were low and similar between treatment groups. Skin bruising was measured throughout the study with no difference noted between treatment groups in the incidence of bruising. The incidence of fractures was 2% in each treatment group.

Concurrent Use with Tiotropium

CLINICAL INFORMATION

Study 1

A 1 year, randomized, parallel-group study conducted at 27 Canadian medical centers compared the efficacy of blinded therapy with either *Advair HFA* or salmeterol added to open-label tiotropium in patients with moderate to severe COPD. Patients included in the study were 35 years or older, had one or more COPD exacerbation requiring treatment with systemic steroids or antibiotics within the previous 12 months and had a 10 plus pack-year smoking history.(53) Patients were also required to have an $FEV_1/FVC < 70\%$ and an $FEV_1 < 65\%$ of predicted. Patients meeting these criteria were randomized to receive one of the following: placebo plus tiotropium 18 mcg once daily, salmeterol 25 mcg via metered dose inhaler (MDI) two inhalations twice daily plus tiotropium 18 mcg once daily, or *Advair HFA* 250/25, two inhalations twice daily plus tiotropium 18 mcg once daily. All medications delivered via an MDI were administered using a spacer device. Tiotropium was delivered using the HandiHaler® device. Patients were allowed to take concurrent COPD medications except inhaled corticosteroids (ICS), long-acting bronchodilators (LABA), and anti-cholinergics. The primary endpoint was the percentage of patients who experienced a COPD exacerbation (defined as treatment with a systemic steroid or antibiotic) within the 1 year study.

There were 449 patients randomized to treatment. Baseline demographics were similar between treatment groups: mean age 68; 54-58% male; mean post-bronchodilator FEV_1 42% of predicted; approximately 50 pack-year smoking history. The majority of patients (73-79%) were receiving ICS or ICS/LABA combination prior to randomization and 46-58% of patients were receiving tiotropium. During the 1 year study 47%, 43% and 26% of patients in the tiotropium, tiotropium plus salmeterol, and tiotropium plus *Advair* groups discontinued study medication (P<0.001 tiotropium vs. tiotropium plus *Advair*) because of

perceived lack of medication efficacy or physician-directed discontinuation of study medication because of a patient's deteriorating health status.

As shown in Table 60 below, there was no statistically significant difference between *Advair HFA* plus tiotropium, salmeterol plus tiotropium, or tiotropium alone in the proportion of patients with one or more COPD exacerbation, mean exacerbations per patient-year, or the number of COPD exacerbations resulting in a physician or ED visit. However, patients receiving *Advair HFA* plus tiotropium (but not salmeterol plus tiotropium) had a significantly fewer COPD exacerbations resulting in hospitalization and hospitalization from any cause compared with tiotropium plus placebo. Additionally, prebronchodilator FEV_1 significantly improved ($P < 0.05$) with *Advair* plus tiotropium (0.086 L) compared with the placebo plus tiotropium (0.027 L). There was no significant difference between salmeterol plus tiotropium and placebo plus tiotropium. Patients receiving either *Advair* plus tiotropium or salmeterol plus tiotropium had significant improvements in quality of life compared with patients receiving placebo plus tiotropium. Changes in the St. George's Respiratory Questionnaire (SGRQ) was –4.5 points in the placebo plus tiotropium, –6.3 points in the salmeterol plus tiotropium group ($P = 0.02$), and –8.6 points in the *Advair* plus tiotropium group ($P = 0.01$). Dyspnea scores did not significantly differ between treatment groups.

Table 60. Results of Primary and Secondary Endpoints for Exacerbation and Hospitalization

Endpoint	Placebo plus tiotropium (n=156)	Salmeterol plus tiotropium (n=148)	*Advair* plus tiotropium (n=145)
≥1 COPD exacerbation, n (%) Absolute Risk Reduction vs. tiotropium plus placebo (95% CI)	98 (62.8) -	96 (64.8) -2.0 (-12.8, 8.8)	87 (60.0) 2.8 (-8.2, 13.8)
Mean exacerbations per patient-year Incidence rate ratio vs. tiotropium plus placebo (95% CI)	1.61 -	1.75 1.09 (0.84, 1.40)	1.37 0.85 (0.65, 1.11)
Urgent HCP or ED visit for COPD Exacerbation, n Incidence rate ratio vs. tiotropium plus placebo (95% CI)	185 -	184 1.06 (0.87, 1.30)	149 0.81 (0.65, 1.01)
Hospitalizations for COPD Exacerbation, n Incidence rate ratio vs. tiotropium plus placebo (95% CI)	49* -	38 0.83 (0.54,1.27)	26* 0.53 (0.33, 0.86)
All-Cause Hospitalizations, n Incidence rate ratio vs. tiotropium plus placebo (95% CI)	62* -	48 0.83 (0.57, 1.21)	41* 0.67 (0.45, 0.99)
* $P<0.05$			

There were 4 deaths in the tiotropium group and 6 deaths in each of the *Advair HFA* plus tiotropium and salmeterol plus tiotropium groups. Serious adverse events were reported in approximately 6% of patients in each treatment group. The most commonly reported adverse events were dry or sore mouth (6.4%, 6.8%, 10.3% for tiotropium, salmeterol plus tiotropium, *Advair* plus tiotropium, respectively), voice hoarseness (0.6%, 1.4%, 6.2%), respiratory failure (4.5%, 2.0%, and 1.4%) and oral candidiasis (0, 0.7%, 4.1%).

Study 2

A "pilot" study was conducted to compare *Advair Diskus* plus tiotropium, *Advair Diskus* alone, and tiotropium alone in patients with stable COPD (FEV_1 <50% of predicted) over a 3-month treatment period.(54) In this study, 90 patients received either the combination of *Advair Diskus* 500/50 given twice a day plus tiotropium 18 mcg given once daily, *Advair Diskus* 500/50 given twice a day, or tiotropium 18 mcg given once daily. The study was conducted using a randomized, double-blind, double-dummy, parallel-group design. Patients were 50 years of age or older (mean ~65 years), current or former smokers (~86% current smokers), with at least a 20 pack-year smoking history (mean ~51 pack years); the mean predicted FEV_1 was 38%. Patients with current evidence of asthma as a primary diagnosis were excluded. Treatments for COPD were discontinued prior to a 2-week run in period except for stable doses of theophylline, and patients were given albuterol for relief of breakthrough symptoms. Patients were

withdrawn from the study if they experienced an exacerbation resulting in hospitalization and/or requiring treatment with oral corticosteroids or antibiotics.

The primary efficacy measure was the mean change from baseline in pre-dose FEV_1 after 3 months of treatment. FEV_1 was measured at monthly intervals. Secondary efficacy measures included change from baseline in dyspnea score, which was analyzed using a visual analog scale, and supplemental albuterol use.

At the end of the study, pre-dose FEV_1 increased significantly in all three treatment groups compared with baseline. The difference between *Advair Diskus* plus tiotropium and either *Advair Diskus* alone or tiotropium alone was significant. The difference between *Advair Diskus* alone and tiotropium alone was not significant. Significant improvements versus baseline were seen in each treatment group for dyspnea scores and albuterol use, but the differences between treatment groups were not significant. See Table 61.

Table 61. Comparison of *Advair Diskus* 500/50 twice daily plus tiotropium 18 mcg once daily versus *Advair Diskus* alone and tiotropium alone(54)

Mean change from baseline	*Advair Diskus* plus tiotropium n = 30	*Advair Diskus* plus placebo n = 30	Tiotropium plus placebo n = 30
FEV_1 (mL)	186*†‡	140*	141*
Dyspnea score (10 point scale)	-2.34*	-2.00*	-2.31*
Albuterol use(puffs per day)	-2.82*	-2.49*	-2.50*
*P<0.05 vs. baseline; †P<0.05 vs. tiotropium alone; ‡P<0.05 vs. *Advair Diskus* alone			

The most common adverse events seen in patients receiving tiotropium were dry mouth, headache, and cough. In patients receiving *Advair Diskus*, throat irritation, hoarseness/dysphonia, headache, and candidiasis of the mouth and throat were the most common events reported. There were no serious adverse events.

Study 3

A randomized, double-blind, 3-way cross-over study compared *Advair Diskus* 500/50 twice daily plus tiotropium 18 mcg once daily ("triple therapy") to the individual treatments (*Advair* alone or tiotropium alone).(201) After a 2-week run-in when patients discontinued existing COPD medications, patients received each study treatment for 2 weeks followed by a 2-week washout period. Patients included in the study were 40-80 years old (mean 63 years), were current or former smokers (47% current smokers) with at least 10 pack-year smoking history (mean 46 pack-years). Patients were also required to have an FEV_1 between 30% and 75% of predicted normal (mean 47%), an FEV_1/FVC ratio of less than 0.7, and symptoms of dyspnea documented by a score of at least 2 on the Modified Medical Research Council Dyspnoea Scale. Forty-one patients were randomized to treatment.

On Day 1 and Day 14 of each two-week treatment period, body plethysmography was performed before study drug administration and at 30, 75, 120, and 240 minutes post-dose. Spirometry was performed pre-dose and 2 and 4 hours post-dose. The primary endpoint was specific airways conductance over the 4 hours ($AUC_{(0\text{-}4\ hr)}$ sGaw) on Day 14. Secondary endpoints included FEV_1, measures of hyperinflation including inspiratory capacity (IC) and residual volume (RV), and dyspnea symptoms measured by the Transition Dyspnea Index (TDI).

In this study, specific airways conductance, FEV_1, and most measures of hyperinflation (including IC and RV) were significantly improved in the triple therapy group compared with the *Advair* and tiotropium groups. Dyspnea scores were statistically and clinically significantly better in the triple therapy group compared with the tiotropium group, but not significantly different than in the *Advair* group. See Table 62.

Table 62. Selected Results at Day 14[201,202]

	***Advair Diskus* plus tiotropium**	***Advair Diskus***	**Tiotropium**
PRIMARY ENDPOINT			
Specific Airway Conductance ($AUC_{(0\text{-}4\ hr)}$ sGaw; L/kPa*s)	0.732	0.575 (*P*<0.001)*	0.600 (*P*<0.001)
SELECTED SECONDARY ENDPOINTS			
Lung function (pre-dose trough FEV_1; L)	1.515	1.303 (*P*<0.001)	1.405 (*P*=0.017)
Hyperinflation: Inspiratory Capacity (2-hour post-dose, L)	2.368	2.150 (*P*<0.001)	2.184 (*P*=0.004)
Hyperinflation: Residual Volume (2-hour post-dose, L)	3.032	3.364 (*P*<0.001)	3.216 (*P*=0.022
Dyspnea (Transition Dyspnea Index [TDI] score)†	2.3	1.6 (*P*=NS)	0.2‡ (*P*<0.001)
Endpoint adjusted geometric mean data at Day 14 unless noted **P* values are comparisons with *Advair Diskus* plus tiotropium based on treatment ratios †Endpoint adjusted mean data; ‡minimal clinically important difference ≥1 unit between treatment groups FEV_1=forced expiratory volume in one second; NS=not statistically significantly different			

The overall incidence of adverse events were similar between treatment groups. Mean blood pressure and pulse rate was also comparable.

8. OTHER STUDIED USES

8.1 Use of *Advair Diskus* 500/50 in COPD

The Torch Study

The TORCH (TOwards a Revolution in COPD Health) study was a three-year, randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational study. [48,203] Key inclusion criteria were:

1. age 40-80 years
2. current or former smoker with a smoking history of ≥10 pack-years
3. forced expiratory volume in one second (FEV_1) ≤ 60% predicted, with ≤10% reversibility in predicted FEV_1
4. FEV_1/forced vital capacity (FVC) ratio of ≤ 70%
5. an established history of chronic obstructive pulmonary disease (COPD) (European Respiratory Society definition[204])

Key exclusion criteria were:

1. current diagnosis of asthma or respiratory disorders other than COPD
2. chest radiograph indicating diagnosis other than COPD
3. previous lung volume reduction surgery or lung transplant
4. requirement for long-term oxygen therapy (greater than 12 hours per day) at start of study
5. receiving long-term oral corticosteroid therapy
6. serious, uncontrolled disease likely to interfere with the study and/or cause death within the three-year study period

Patients were randomized to twice-daily treatment with either *Advair Diskus*500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo for three years. They were also stratified according to smoking status to ensure balanced treatment allocation. All study medications were administered using the Diskus®

device. All inhaled corticosteroids (ICS) and inhaled long-acting bronchodilators (beta-adrenergics and anticholinergics) were discontinued at entry to the two-week run-in period. Patients were allowed to take any COPD concomitant medication except ICS, long-acting bronchodilators (beta-adrenergics and anticholinergics), and long-term oral corticosteroids. All patients were offered albuterol as relief medication.

Patients who withdrew from the study were eligible to receive any alternative therapy subsequently. However, they were followed for vital status for the entire three-year study period as part of the originally-assigned treatment group.

The primary endpoint was all-cause mortality for the comparison of *Advair Diskus* with placebo. The survival status of each patient, regardless of their continued participation in the study, was noted every three months until three years had elapsed since randomization. Secondary endpoints were rate of COPD exacerbations and health status as measured by the St. George's Respiratory Questionnaire. Other mortality and exacerbation end-points, requirements for oxygen therapy, clinic lung function, and safety end-points including adverse events and bone fracture information were evaluated.

The study was guided by a Steering Committee consisting of external clinical experts and representatives of GlaxoSmithKline. An independent Safety and Efficacy Data Monitoring Committee oversaw ethical and safety issues, and they reviewed cumulative serious adverse events data every 6 months. An Endpoint Committee independently reviewed and categorized the cause of death for each patient where a death was recorded.

Patient disposition is summarized in Table 63. The incidence of study medication discontinuation was significantly greater in the placebo, salmeterol and FP groups than in the group of patients treated with *Advair Diskus*.[48]

Table 63. Patient Disposition in the TORCH Study at 3 Years [48]

	Placebo n=1544	Salmeterol n=1542	Fluticasone Propionate n=1552	*Advair Diskus* 500/50 n=1546
Patients Withdrawing from the Study	44.2%	36.9%	38.3%	34.1%

In this study, 6184 patients were randomized to treatment; 6112 patients were included in the efficacy analysis (*Advair Diskus* n=1533, FP n=1534, salmeterol n=1521, placebo n=1524), and all 6184 patients were included in the safety analysis (*Advair Diskus* n = 1546, FP n = 1552, salmeterol n = 1542, placebo n = 1544). The mean age of the patients was 65 years, 76% were male, the mean post-bronchodilator FEV_1 was 44% of predicted, and 43% of the patients were current smokers.[48]

Survival

The primary analysis was log-rank analysis of time to death from any cause by 3 years for patients randomized to *Advair Diskus* vs. placebo, regardless of how long they took treatment (i.e., conservative strict intention-to-treat analysis). This final analysis was adjusted for 2 interim analyses which were carried out by the Safety and Efficacy Data Monitoring Committee while the study was still ongoing. *Advair Diskus* reduced the risk of dying at any time in the three years by 17.5% vs. placebo (*P*=0.052) (percentage of deaths 12.6% vs. 15.2%, respectively). See Table 64. There was also a trend to reduction in COPD-related mortality with *Advair Diskus* (4.7%) vs. placebo (6.0%) (HR 0.78, 95% CI 0.57-1.06, *P*=0.107). It is not known to what extent the possible selection of active treatment following study discontinuation by the placebo group may have influenced these results.[48]

Table 64. Effect of *Advair Diskus* 500/50 on all-cause mortality over three years in COPD[48,205]

Analysis	Hazard Ratio *Advair*/Placebo	95% CI	*P* value
Log rank adjusted for 2 interim analyses	0.825	0.681-1.002	0.052
Log rank unadjusted	0.820	0.677-0.993	0.041*
Cox's proportional hazards	0.811	0.670-0.982	0.031
*to be compared with a significant level of 0.04 because of the interim analyses; CI=confidence interval			

Salmeterol 50 mcg twice daily and fluticasone propionate (FP) 500 mcg twice daily were not significantly different compared to placebo (salmeterol HR 0.879, 95% CI 0.729-1.061; FP HR 1.060, 95% CI 0.886-1.268). No significant interactions by baseline FEV_1 (<30%, 30-50%, ≥50% of predicted), smoking status, age, body mass index, or sex were found ($P \geq 0.12$).[48]

Exacerbation Results

A history of exacerbations was not required for patients entering the study, but 57% of patients had experienced at least one COPD exacerbation in the year prior to the study. The rate of moderate/severe exacerbations was evaluated as a secondary outcome in this study. Exacerbations were defined as moderate if they were treated with antibiotics and/or systemic corticosteroids and severe if hospitalized. Over 13,000 exacerbations were recorded in the study. The mean rate of moderate/severe exacerbations per annum was 0.85 for *Advair Diskus,* 0.93 for fluticasone propionate (FP), 0.97 for salmeterol, and 1.13 for placebo. The rate of moderate/severe exacerbations was reduced by 25% in the *Advair Diskus* group compared to placebo ($P<0.001$).[48]

Table 65. Effect of *Advair Diskus* 500/50 on exacerbations over three years in COPD [48]

	Treatment Difference		
	***Advair Diskus 500/50* vs. placebo (95% CI)**	***Advair Diskus 500/50* vs. salmeterol 50 mcg (95% CI)**	***Advair Diskus 500/50* vs. FP 500 mcg (95% CI)**
Moderate/Severe* exacerbation rate ratio	0.75 (0.69, 0.81) ($P<0.001$)	0.88 (0.81, 0.95) ($P=0.002$)	0.91 (0.84, 0.99) ($P=0.024$)
*moderate: antibiotics and/or systemic corticosteroids; severe: hospitalization; CI=confidence interval; FP=fluticasone propionate			

Both components were also significantly more effective than placebo (18% and 15% reduction vs. placebo for FP and salmeterol respectively; both $P<0.001$). The rate of exacerbations treated with systemic corticosteroids was reduced with *Advair Diskus* by 43% compared with placebo ($P<0.001$), by 13% compared with FP ($P=0.017$), and by 29% compared with salmeterol ($P<0.001$). *Advair Diskus* reduced the rate of severe exacerbations by 17% ($P=0.028$ vs. placebo).[48]

The number needed to treat to prevent one exacerbation per year was 4. The number needed to treat to prevent one hospitalization per year was 32.[48]

Quality of Life/Health Status

Of the 6112 subjects in the TORCH study, health status measured by the St. George's Respiratory Questionnaire (SGRQ) was assessed as a secondary endpoint in 4951 patients from countries with a validated questionnaire (*Advair Diskus* n=1240, FP n=1248, salmeterol n=1232, placebo n=1231). Scores were analyzed as mean differences over the 3-year study period.

Adjusted mean changes from baseline to 156 weeks were:*Advair Diskus* -3.0; FP -1.8; salmeterol -0.8; and placebo +0.2. *Advair Diskus* resulted in a statistically significant improvement in quality of life score when compared to placebo as measured by the SGRQ ($P<0.001$). The difference in the SGRQ score between *Advair Diskus* and placebo was 3.1 points; 4 points is considered a clinically significant difference.[48] See Table 66.

Table 66. Effect of *Advair Diskus* 500/50 on health status over three years in COPD[48]

	Treatment Difference		
	***Advair Diskus 500/50* vs. placebo (95% CI)**	***Advair Diskus 500/50* vs. Salmeterol 50 mcg (95% CI)**	***Advair Diskus 500/50* vs. FP 500 mcg (95% CI)**
SGRQ total score (units)	-3.1 (-4.1, -2.1) (*P*<0.001)	-2.2 (-3.1, -1.2) (*P*<0.001)	-1.2 (-2.1, -0.2) (*P*=0.017)
CI = confidence interval; SGRQ=St. George's Respiratory Questionnaire (a change in score of 4 units has been determined to be clinically significant)			

Advair Diskus also showed the greatest treatment benefits over placebo in all domain scores (Symptoms -3.6 units, Activity -2.8 units, Impact -3.2 units; all *P*<0.001). In the responder analysis, *Advair Diskus* patients were more likely to be improved or maintained compared with placebo (58% vs. 42% improving or maintained; *P*<0.001). The same was true for *Advair Diskus* vs. its components (FP = 52%, salmeterol = 49% improving or maintained; *P*≤0.006 vs. *Advair Diskus*).[206]

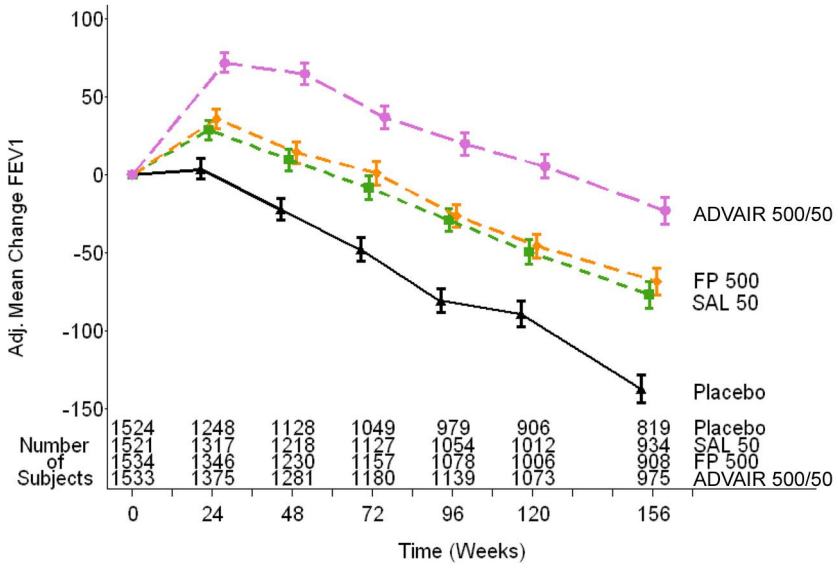
Lung Function

Lung function was a tertiary endpoint in the TORCH study.[48,205] Lung function, as measured by postbronchodilator FEV_1, was significantly improved with *Advair Diskus* compared with placebo. See Table 67 and Figure 27. Over the entire three-year treatment period, improvements in postbronchodilator FEV_1 were larger in the *Advair Diskus* group than the placebo group and both of the other active treatment groups (*P*<0.001). Mean FEV_1 was also higher than placebo for both the salmeterol and FP groups (*P*<0.001).

Table 67. Postbronchodilator FEV_1 in the 3-Year TORCH Study[48,205]

Postbronchodilator FEV_1	**Placebo n=1261**	**Salmeterol 50 mcg n=1334**	**FP 500 mcg n=1356**	***Advair Diskus 500/50* n-1392**
Adjusted mean change from baseline, averaged over three years	-62.3 mL	-20.9 mL	-15.0 mL	29.2 mL
Treatment difference vs. placebo (*P*-value)		41.5 mL (*P*<0.001)	47.4 mL (*P*<0.001)	91.5 mL (*P*<0.001)
Treatment difference vs. *Advair Diskus* (*P*-value)		50.1 mL (*P*<0.001)	44.2 mL (*P*<0.001)	
Note: Repeated measures analysis adjusted for smoking status, age, sex, baseline FEV_1, Body Mass Index (BMI), world geographic region, visit, baseline FEV_1 by visit, and treatment group by visit.				

Figure 27. Adjusted Mean Change in Post-Bronchodilator FEV_1 over Time in the 3-Year TORCH Study[48]

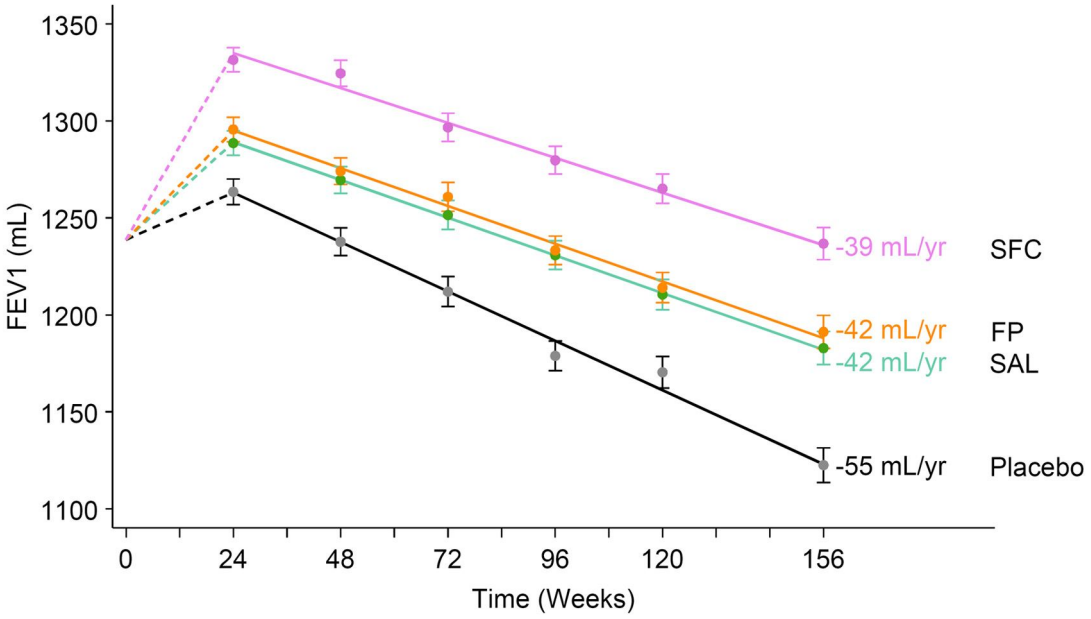


A *post hoc* analysis was performed to investigate the effects of treatment on rate of decline in FEV_1.[49] See Table 68 and Figure 28. Rate of decline was reduced by all active treatments compared with placebo ($P \leq 0.003$). There was no difference observed between *Advair Diskus* and either salmeterol or FP.

Table 68. Rate of Decline (mL/year) in Postbronchodilator FEV_1 in the 3-Year TORCH Study[49]

	Placebo (n=1261)	**Salmeterol 50 mcg n=1334**	**FP 500 mcg n=1356**	***Advair Diskus 500/50* n-1392**
Adjusted rate of decline	-55.3 mL/year	-42.3 mL/year	-42.3 mL/year	-39.0 mL/year
Treatment difference vs. placebo (*P*-value)		13.0 mL/year (*P*=0.003)	13.0 mL/year (*P*=0.003)	16.3 mL/year (*P*<0.001)
Treatment difference vs. *Advair Diskus* (*P*-value)		3.3 mL/year (*P*=0.441)	3.3 mL/year (*P*=0.445)	
Note: Random coefficients model adjusted for smoking status, age, sex, baseline FEV_1, world geographic region, and time on treatment.				

Figure 28. Rate of Decline (mL/year) in Post-Bronchodilator FEV_1 in the 3-Year TORCH Study[172]



Safety

Total treatment-years exposure was 3700 for *Advair Diskus*, 3555 for fluticasone propionate (FP), 3531 for salmeterol, and 3278 for placebo.[48]

There were more pneumonias reported in steroid-containing arms. The three-year probability of having pneumonia reported as an adverse event was 19.6% for *Advair Diskus* vs. 12.3% for placebo ($P<0.001$). The numbers of on-treatment pneumonia deaths were similar (*Advair Diskus* n=8, placebo n=7).[48]

The incidence of hypothalamic-pituitary-adrenal (HPA) axis adverse events was low (*Advair Diskus* n=0, FP n=2, salmeterol n=0, placebo n=2).[207] There was no increased cardiac adverse events reported on any treatment compared with placebo. No significant difference in development of cataracts, glaucoma, or related disorders was found between groups and placebo during the study. Conclusions about cataracts cannot be drawn from this study because the high incidence of cataracts at baseline (61% to 71%) resulted in an inadequate number of patients treated with *Advair Diskus* 500/50 who were eligible and available for evaluation of cataracts at the end of the study (n = 53).[48]

There was no significant difference in probability of bone fracture (*Advair Diskus* 6.3% vs. placebo 5.1%) and no difference in non-traumatic fractures (*Advair Diskus* 1.7% vs. placebo 1.8%). In the U.S. subset, adjusted percent change in bone mineral density (BMD) at 3 years (total hip) was -3.2% for *Advair Diskus*, -2.9% for FP, -1.7% for salmeterol, and -3.1% for placebo (all $P>0.05$). Conclusions regarding BMD cannot be drawn from this study because of the large number of drop outs (>50%) before the end of the follow-up and the maldistribution of covariates among the treatment groups that can affect BMD.[48]

The most frequently reported adverse events reported during treatment with a study medication are shown in Table 69. The most common event was COPD exacerbations.

Table 69. Most Frequently Reported Adverse Events During Treatment with *Advair Diskus* 500/50 in COPD over three years[48]

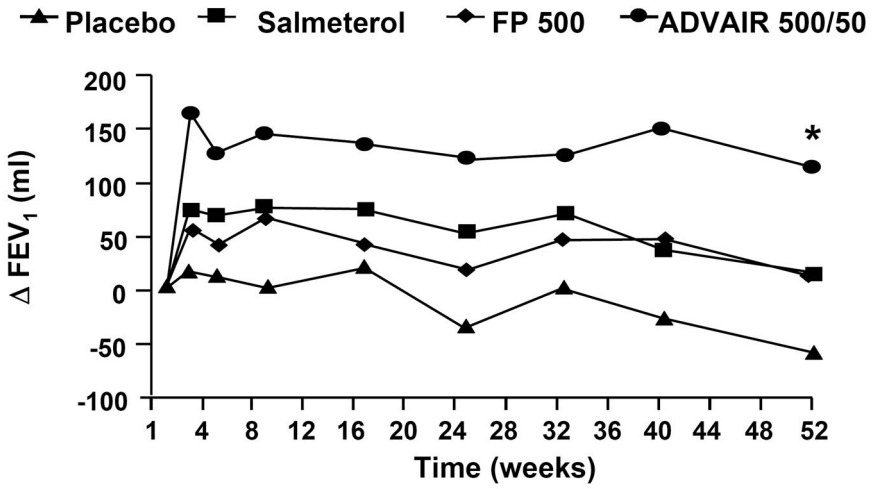
Rate per Year	Placebo (n=1544)	Salmeterol 50 mcg (n=1542)	FP 500 mcg (n=1552)	*Advair Diskus* 500/50 (n=1546)
COPD exacerbation	0.92	0.76	0.78	0.67
Upper respiratory tract infection	0.10	0.08	0.09	0.11
Nasopharyngitis	0.09	0.09	0.10	0.10
Pneumonia	0.04	0.04	0.07	0.07
Bronchitis	0.05	0.05	0.05	0.05
Headache	0.08	0.06	0.06	0.05
Back pain	0.04	0.04	0.04	0.04
Sinusitis	0.03	0.03	0.04	0.04
Cough	0.03	0.03	0.04	0.03
Hypertension	0.03	0.03	0.03	0.02
FP = fluticasone propionate				

The TRISTAN Study - Advair Diskus 500/50 12-Month Study

The TRISTAN (TRial of Inhaled Steroids ANd long-acting β_2 agonists) study was a one-year, randomized, double-blind, placebo-controlled, parallel-group, multicenter study.[157] A total of 1465 patients with chronic obstructive pulmonary disease (COPD) (prebronchodilator forced expiratory volume in one second [FEV_1] 25-70% of predicted) were randomized to one year of twice-daily treatment with either *Advair Diskus 500/50*, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo. The primary endpoint was change in lung function (FEV_1).

Results showed that patients receiving *Advair Diskus 500/50* had a significantly greater improvement at endpoint in pre-dose FEV_1 (113 mL) compared to those receiving FP 500 mcg (7 mL, $P < 0.0001$), salmeterol 50 mcg (15 mL, $P < 0.0001$), and placebo (-60 mL, $P < 0.0001$).[157] These increases in pre-dose FEV_1 corresponded with mean percent changes from baseline of 10% for *Advair Diskus 500/50* , 2% for FP 500 mcg, 2% for salmeterol 50 mcg, and –3% for placebo (Figure 29). Similar trends were seen for other measures of lung function (post-bronchodilator FEV_1, peak expiratory flow).

Figure 29. Mean Change from Baseline of Pre-dose FEV_1 (mL) in the 1-Year TRISTAN Study[158]



**P*<0.0001 *Advair Diskus* vs. placebo, salmeterol, and FP

Approximately 50% of patients experienced at least one exacerbation during the study.[157] The average number of moderate and/or severe exacerbations per year in the group receiving *Advair Diskus 500/50* was 0.97 compared to 1.30 in the placebo group ($P<0.001$, representing a 25% reduction) compared to 1.04 in the salmeterol group ($P=0.003$ versus placebo) and 1.05 in the FP group ($P=0.003$ versus placebo). The difference in the rate of exacerbations between *Advair Diskus* and the individual components was not statistically significant. In addition, the number of exacerbations requiring oral steroids was reduced by 39% with *Advair Diskus 500/50* , 29% with salmeterol 50 mcg, and 34% with FP 500 mcg ($P<0.0003$ vs. placebo for all).

Patients receiving *Advair* 500/50 also had significantly reduced breathlessness and use of relief medication compared with the individual components and placebo (Table 70).[157] No significant difference was noted in the other symptoms measured with *Advair* compared with the other treatment arms except cough which was significantly reduced compared with placebo. Additionally the mean number of nighttime awakenings was significantly reduced with *Advair* compared with salmeterol and placebo. Quality of Life scores using the St. George's Respiratory Questionnaire (SGRQ) were statistically significantly improved among patients receiving *Advair* compared with FP (treatment difference -1.4; $P = 0.021$) and placebo (treatment difference -2.2; $P < 0.001$), although the difference between treatment groups did not exceed the minimal clinically important difference of 4 units.[158] At one year, a clinically significant improvement from baseline in SGRQ was only achieved in the *Advair* treatment group (mean change -4.5).

Table 70. TRISTAN: Results of Secondary Endpoints[157,158]

	Advair Diskus 500/50	**FP 500 mcg**	**Salmeterol 50 mcg**	**Placebo**
Symptoms Scores				
Cough	1.35*	1.38	1.36	1.44
Breathlessness	1.47*†‡	1.58	1.59	1.66
Sputum Production	1.29	1.33	1.30	1.34
Sputum Color	1.32	1.37	1.35	1.36
Median Use of Relief Medication (range)	1 (0-10)*†‡	2 (0-11)*	2 (0-14)*	2 (0-32)
Mean Number of Awakenings Per Week	2.31*‡	2.45*	2.94	3.01
SGRQ, Mean Change from Baseline at Week 52	-4.5	-2.8	-2.4	-2.8
*$P < 0.05$ vs. Placebo †$P < 0.05$ vs. FP ‡$P < 0.05$ vs. Salmeterol				

The most commonly occurring adverse events were exacerbation of COPD (*Advair Diskus* group 49%; placebo group 53%) and upper respiratory tract infection (12% vs. 12%). Pneumonia was reported in 5% of *Advair Diskus* patients and 2% of placebo patients.

Serum cortisol was measured at 0, 24, and 52 weeks. Throughout the study the percentage of patients who had changes from within to below the normal reference range were 4% (*Advair*), 4% (placebo), 5% (salmeterol) and 6% (FP).[157] At the end of the 1-year study, mean cortisol concentrations increased by 4% and 6% in the placebo and salmeterol groups, respectively and fell by 1% and 3% with FP and *Advair*, respectively. The difference between FP and placebo were statistically significant at weeks 24 and 52. The difference between *Advair* and placebo were statically significant at week 24. None of the changes were associated with any clinical symptoms. There were no treatment-related echocardiogram changes detected during the study.

Advair Diskus 500/50 – 44-Week Study

A randomized, double-blind, parallel-group study compared the effect of *Advair Diskus* 500/50 vs. salmeterol 50 mcg each administered twice daily via the Diskus® device on exacerbations (primary endpoint) in patients with chronic obstructive pulmonary disease (COPD). Patients were at least 40 years of age, had a post-bronchodilator forced expiratory volume in one second (FEV_1) less than 50% of predicted, an FEV_1/forced vital capacity (FVC) ratio of 70% of predicted or less, smoking history of at least 10 pack-years, and a documented history of two or more moderate to severe COPD exacerbations during the last year before the study. Moderate exacerbations were defined as worsening of COPD symptoms that required a change in respiratory medications and medical assistance; severe exacerbations were defined as those resulting in hospitalization or emergency room treatment.(208)

A total of 507 patients received *Advair Diskus* 500/50 and 487 patients received salmeterol. The mean age was 64 years, and the mean FEV_1 was 40% of predicted. The mean number of moderate/severe exacerbations in the previous years was 2.9.(208)

Exacerbation Results

The number of moderate plus severe exacerbations was significantly reduced in the group treated with *Advair Diskus* vs. salmeterol (334 exacerbations in 210 patients vs. 464 exacerbations in 241 patients, respectively; $P<0.0001$). The annualized exacerbation rate was significantly lower in the group treated with *Advair Diskus* vs. salmeterol, (0.92 and 1.4, respectively; $P<0.0001$), corresponding to an estimated treatment effect ratio of 0.65 (95% CI, 0.57-0.76) which translates into a 35% reduction of the mean exacerbation rate. The mean time to first exacerbation was significantly longer in the group treated with *Advair Diskus* vs. salmeterol (128 vs. 93 days, $P<0.0001$). The number of patients needed-to-treat with *Advair Diskus* vs. salmeterol to prevent one moderate/severe exacerbation per year was 2.08.(208)

Other secondary endpoints evaluated included lung function and changes in SGRQ scores.(208) Patients receiving *Advair* and salmeterol had improvements in post-bronchodilator FEV_1 (0.07 L and 0.05 L, respectively); however, there was no significant difference between treatments. Improvements in mean morning pre-brochodilator PEF were significantly improved with *Advair* compared with salmeterol alone (18.0 L/min vs. 4.4 L/min; $P < 0.0001$). Additionally, the mean SGRQ total score was improved with *Advair* compared with salmeterol, and this difference did reach statistical significance (treatment difference -2.3; $P= 0.0126$).

Drug-related adverse events were noted in 9.7% of cases in the *Advair Diskus* group and 8.2% in the salmeterol group. Oropharyngeal candidiasis was the most frequent drug-related adverse event in the *Advair Diskus* group (n=8). Twenty-three cases of suspected pneumonia were observed in the *Advair Diskus* group and seven in the salmeterol group.(208)

8.2 Effect of *Advair* on Asthma Control: The GOAL Study

Gaining Optimal Asthma Control (GOAL) Study

The Gaining Optimal Asthma controL (GOAL) study was a 1-year, randomized, stratified, double-blind, parallel-group prospective trial in 3421 patients with uncontrolled asthma that compared the safety and efficacy of individual, pre-defined, step-wise increases of *Advair Diskus* or fluticasone propionate (FP) alone in achieving two pre-defined, composite measures of asthma control: well-controlled and totally controlled asthma. (10) The primary endpoint was the percentage of patients who achieved well-controlled asthma in Phase I.

Both definitions of control were derived from the treatment guidelines of the Global Initiative for Asthma (GINA)(209) and National Institutes of Health (NIH)(210) and were composite measures of several asthma outcomes (Table 71). (10) In order to achieve a totally controlled or well-controlled week, patients had to meet all of the specified criteria for that week. Totally controlled was defined as having totally controlled asthma for 7 weeks during the 8 consecutive week assessment. Well-controlled was defined as having well-controlled asthma for 7 weeks during the 8 consecutive week assessment. An exacerbation, emergency room visit, or treatment-related adverse event resulted in the automatic failure of control status for the entire 8-week assessment regardless of asthma control during other time points of the assessment.

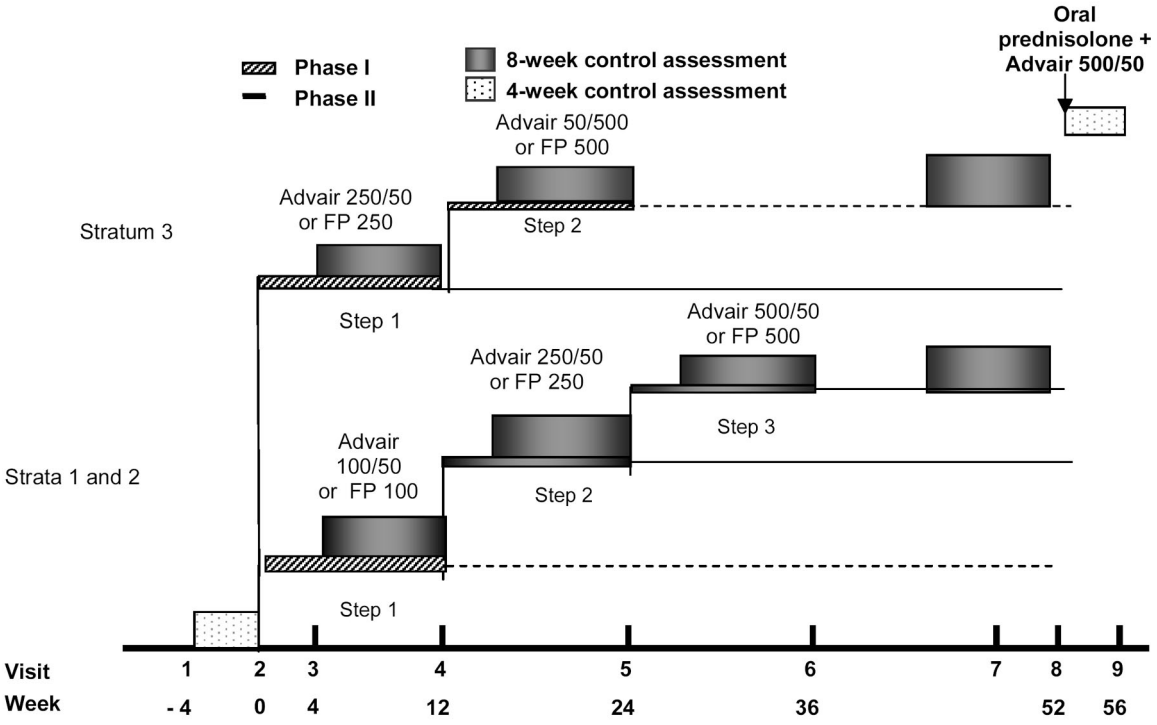
Table 71. Definitions of Well-Controlled or Totally-Controlled Asthma Based on GINA and NIH Guidelines Goals of Therapy (1)

	TOTALLY CONTROLLED	**WELL-CONTROLLED**
Each Week*	**All of:**	**Two or more of:**
Daytime symptoms	None	≤ 2 days with symptom score of > 1
Rescue β_2-agonist use	None	Use on ≤ 2 days and ≤ 4 occasions/ week
Morning PEF	≥ 80% predicted every day	≥ 80% predicted every day
	All of:	**All of:**
Nighttime awakenings	None	None
Exacerbations	None	None
Emergency visits	None	None
Treatment-related adverse events	None enforcing change in asthma therapy	None enforcing change in asthma therapy
*Maintained for at least 7 out of 8 weeks		

During the 4-week run-in period, patients on inhaled corticosteroids (ICS) at baseline continued on their usual dose. Patients who did not achieve at least 2 well-controlled weeks during the run-in period were randomized to one of three strata based on their dose of ICS during the 6 months prior to screening: stratum 1 included patients on no ICS; stratum 2 included patients on ≤ 500 mcg of beclomethasone dipropionate daily or equivalent; and stratum 3 included patients on > 500 mcg to 1000 mcg of beclomethasone dipropionate daily or equivalent.

Furthermore, there were two phases of the study. During phase I, or the dose escalation phase, twice daily doses of *Advair Diskus* and fluticasone propionate (FP) were increased every 12 weeks until totally controlled asthma was achieved or the highest dose of either treatment was reached (*Advair Diskus* 500/50 twice daily or FP 500 mcg twice daily) (Figure 30). After achieving totally controlled asthma or after 12 weeks on the maximum dose of study medication, patients entered phase II of the study for the remainder of the 1-year, double-blind treatment period. During phase II, patients remained on either the dose in which they achieved totally controlled asthma or the highest dose of study medication. No step down therapy occurred during phase II of the study in order to assess the incremental effect of time on the attainment of asthma control.

Figure 30. Dose Escalation Parameters for Strata 1, 2, and 3 in Phases I and II (1)



Patients who did not achieve totally controlled asthma during phase I were reevaluated at the end of phase II. Patients who had not achieved totally controlled asthma by the end of phase II were enrolled in a 4-week, open-label phase during which all patients received oral prednisolone (0.5 mg/kg to 60 mg/day for 10 days) and *Advair Diskus* 500/50 twice daily for 4 weeks.

Patients included in the study were between 12 and 80 years of age with at least a 6 month history of asthma who had an improvement in FEV_1 of ≥ 15% and ≥ 200 ml after inhalation of a short-acting $beta_2$-agonist. In addition, patients had to have a smoking history of less than 10 pack-year and no use of long-acting inhaled or oral $beta_2$-agonist within the previous 2 weeks. Baseline demographics and characteristics were similar between treatment groups within each stratum (Table 72).

Table 72. Baseline Characteristics

Strata	Stratum 1 No ICS at Entry		Stratum 2 BDP ≤500 mcg/day at Entry		Stratum 3 BDP >500 - ≤1000 mcg/day at Entry	
	Advair (n = 548)	FP (n = 550)	*Advair* (n = 585)	FP (n = 578)	*Advair* (n = 576)	FP (n = 579)
Mean age, y	36.1	36.4	40.4	40.3	44.1	42.7
Female, %	57	57	58	60	57	59
Mean prebronchodilator FEV_1, % predicted	77	79	78	77	75	76
Rescue medication use, mean occasions/day	1.9	1.7	1.7	1.7	1.9	1.9
Mean daily symptom score*	1.8	1.7	1.8	1.8	1.9	1.9
Nighttime awakenings, mean occasions/night	0.6	0.6	0.4	0.4	0.5	0.5
Exacerbation rate†	0.4	0.3	0.6	0.5	0.7	0.7

BDP = beclomethasone dipropionate

*Symptom scores were based on a scale of 0 (none) to 5 (severe).

† Documented episodes of hospitalization and/or course of oral steroids or antibiotics for the treatment of an exacerbation of asthma during the past 12 months.

Results

Of the 3416 patients enrolled in the study, a total of 3039 patients completed phase I, and 2890 completed phase II. In both phase I and phase II, a significantly greater proportion of patients achieved totally controlled asthma and well-controlled asthma in the *Advair Diskus* group compared with FP. During phase 1, the proportion of patients achieving well-controlled or totally controlled asthma at the same or lower dose of ICS was greater in the *Advair Diskus* group compared with FP in each stratum (Figure 31 and Figure 32). In both treatment groups, control was maintained throughout phase II of the study by the majority of patients achieving control during phase I.

Figure 31. Dose of Treatment at Which Totally Controlled Status was Achieved (Phase I)

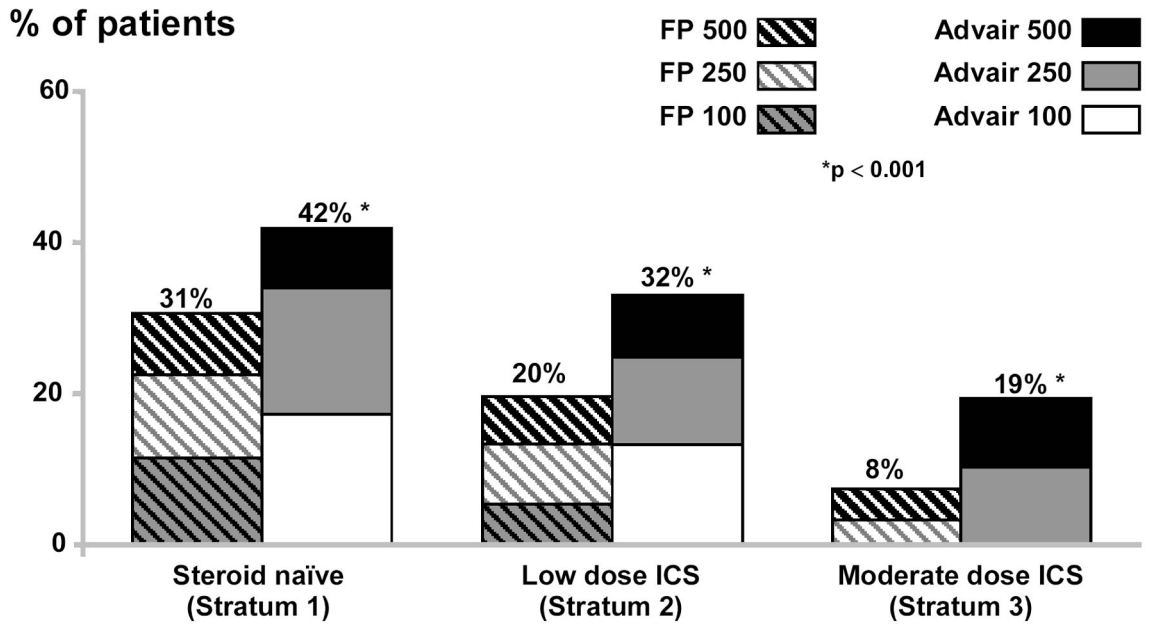
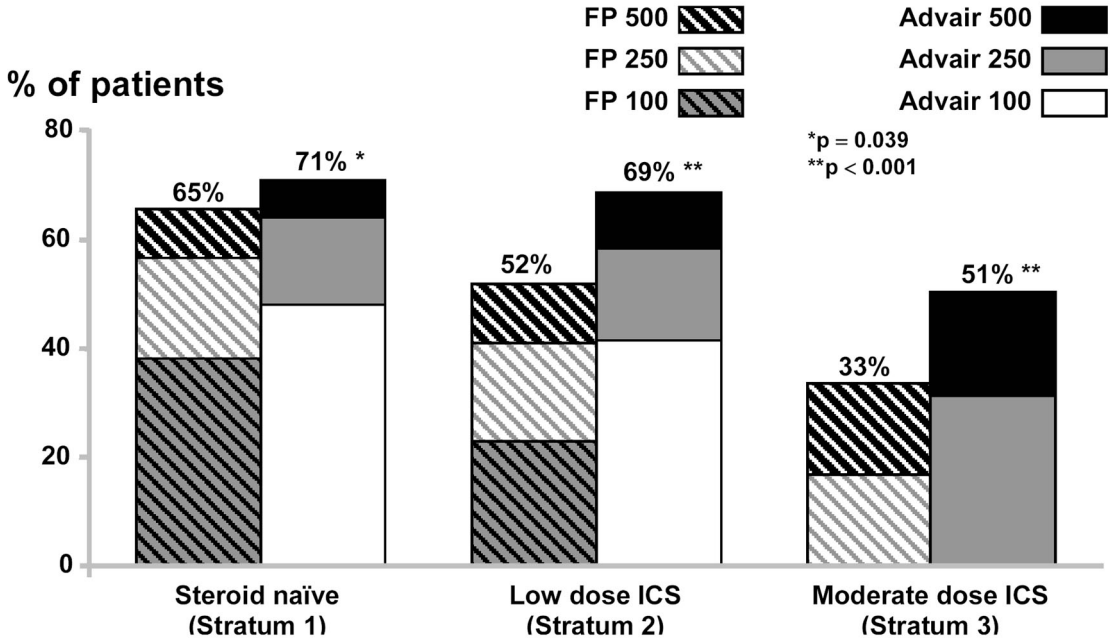


Figure 32. Dose of Treatment at Which Well-Controlled Status was Achieved (Phase I)



Time to Achieve Control

An analysis of time to asthma control was conducted during Phase I. Time to asthma control was defined as time to the first well-controlled or totally controlled week. Patients receiving *Advair Diskus* achieved control significantly faster than patients receiving FP alone ($P \leq 0.002$). The week by which 50% of patients achieved their first well-controlled week during phase I was significantly faster with *Advair Diskus* compared with FP ($P < 0.001$) for all three strata. In addition, the week by which 50% of the patients achieved their first totally controlled week during the entire 52-week study period was faster with *Advair Diskus* compared with FP. Results shown in Table 73.

Table 73. Analysis of Time to Asthma Control

	Stratum 1		Stratum 2		Stratum 3	
	Advair	**FP**	***Advair***	**FP**	***Advair***	**FP**
Time to achieve totally controlled asthma, weeks (over 1-year study period)§	16	24	21	45	38	–‡
Time to achieve well-controlled asthma, weeks (over weeks 1-12)§	3†	4	2†	7	5†	10

§ Time to control (weeks) for 50% of patients

‡ Less than 50% of patients achieved a totally controlled week

† $P < 0.001$

Maintenance of Asthma Control

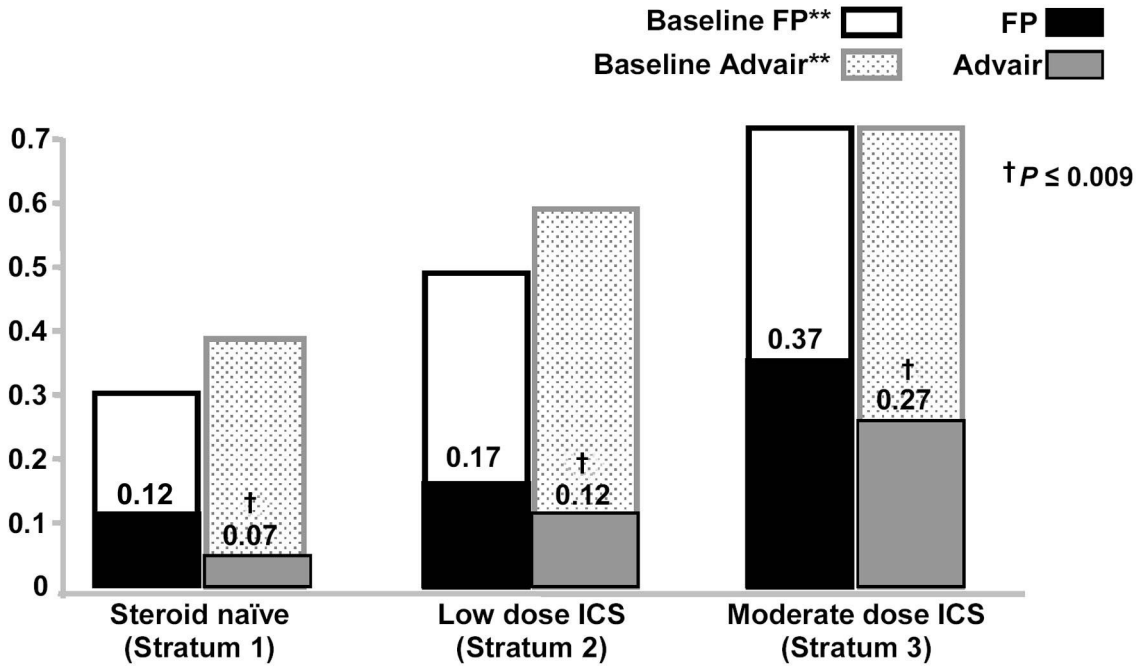
A post-hoc analysis of 846 patients who achieved totally-controlled asthma in phase I found that total control was maintained for a mean of 12-14 weeks and at least well-controlled asthma was maintained for a mean of 21-24 weeks during phase II.[211] In addition, 20 - 23% of patients achieving totally controlled asthma maintained total control for the entire double-blind treatment period. Patients who achieved well-controlled asthma by the end of phase I (n = 1017) maintained at least well-controlled asthma for a mean of 11-14 weeks. Of the patients who achieved well-controlled or totally controlled asthma in phase II, at least well-controlled asthma was maintained for more than 85% and 95% of weeks of phase II, respectively.

Patients who achieved a higher level of asthma control during phase I were more likely to achieve control during phase II of the study. Patients who achieved total control by the end of phase 1 were 31 times more likely to be totally controlled during phase II compared with patients who were not well controlled and 7 times more likely compared with patients who were well-controlled at the end of phase I. Treatment type also affected the likelihood of achieving asthma control. After adjusting for control status at the end of phase I, patients receiving *Advair* were 1.2 times more likely to be totally controlled and 1.27 times more likely to be at least well-controlled than patients receiving FP alone ($P \leq 0.007$ for both endpoints).

Effect of Treatment on Exacerbations

The mean annual rate of exacerbations requiring oral corticosteroids and/or hospitalization or emergency visits was significantly lower in the *Advair Diskus* group compared with FP in all strata ($P \leq 0.009$) (Figure 33). [10] The rate of exacerbations was 40% lower in stratum 1, 29% lower in stratum 2, and 26% lower in stratum 3 in the *Advair Diskus* group compared with the FP group. There was a trend towards the reduction in the annual rate of exacerbations during phase II compared with phase 1 of the study. In addition, patients who achieved totally and well-controlled asthma during phase I had lower annualized exacerbation rates (0.05 and 0.13, respectively) compared with patients who remained uncontrolled (0.23).

Figure 33. Mean Rate of Exacerbations over Weeks 1-52



In a combined analysis of all 3 strata, a total of 262 (15%) of patients in the FP group and 178 (10%) of patients in the *Advair Diskus* group experienced at least one exacerbation that required treatment with either oral corticosteroids, hospitalization or an emergency room visit. The mean number of exacerbations per patient per year for the combined analysis was 0.14 for *Advair Diskus* and 0.19 for FP resulting in a 29% reduction in the exacerbation rate for patients receiving *Advair Diskus* compared with patients receiving FP.

Individual Asthma Outcomes

Across all strata, patients receiving *Advair Diskus* had greater improvements in PEF, symptom scores, symptom-free days and rescue-free days compared with patients receiving FP alone.[212] Results for these individual outcomes are presented in Table 74 below. Additionally the mean number of nighttime awakenings was significantly less with *Advair Diskus* compared with FP alone ($P < 0.05$).

Table 74. GOAL: Results of Individual Asthma Outcomes Evaluated Over Weeks 1-52

	Stratum 1 (ICS Naïve)		Stratum 2 (Low Dose ICS)		Stratum 3 (Medium Dose ICS)		Pooled Strata	
	Advair	**FP**	***Advair***	**FP**	***Advair***	**FP**	***Advair***	**FP**
PEF, Adjusted Mean Change (L/min)	71.1*	49.2	57.1*	30.0	45.7*	21.6	58.2*	33.9
Symptom scores, Adjusted Mean Change	-1.2*	-1.0	-1.1*	-0.8	-0.9*	-0.6	-1.0*	-0.8
Symptom-free days, Median %	81.5	76.6	74.2	51.0	55.9	29.9	72.5	54.5
Symptom-free days, OR (95% CI)	1.30† (1.03, 1.64)		2.06* (1.66, 2.56)		1.78* (1.43, 2.21)		1.69* (1.49, 1.92)	
Rescue-free days, Median %	91.8	87.1	87.8	72.0	77.9	61.9	87.3	74.7
Rescue-free days, OR (95% CI)	1.64* (1.27, 2.12)		2.24* (1.78, 2.82)		1.85* (1.48, 2.30)		1.91* (1.67, 2.18)	

Symptom scores were rated on a scale of 0 (no symptoms) to 5 (symptoms of sufficient severity to prevent the patient working or performing normal daily activities).

*$P < 0.001$; †$P = 0.025$

Adverse Events and Urinary Cortisol

Adverse events were similar between treatment groups. Serious adverse events were reported in 4% of patients receiving *Advair Diskus* and 3% of patients receiving FP. The most common serious adverse events included asthma and pneumonia (< 1% for both treatment groups, respectively). The most commonly reported drug-related adverse events for *Advair Diskus* and FP, respectively, included oral candidial infections (3% in both groups), hoarseness (3% versus 2%), and pharyngolaryngeal pain (< 1% versus 1%). Urinary cortisol levels were evaluated for a small subset (n = 194) of patients in which baseline and endpoint data were available. The baseline and week 52 values for the geometric mean of the cortisol/creatinine ratio (nmol/mmol) were 3.74 and 3.04 for *Advair Diskus* and 3.92 and 2.85 for FP. There was no statistical difference in geometric means of the cortisol/creatinine ratio at week 52 for *Advair Diskus* compared with FP ($P = 0.318$). In patients receiving the highest dose of ICS (500 mcg), the geometric means were similar between treatment groups at baseline and endpoint (3.76 versus 2.90 for *Advair Diskus* and 3.82 versus 2.73 for FP).

8.3 Use of *Advair* as Initial Maintenance Therapy in Asthma

A 12-week, randomized, double-blind, multicenter study was conducted in 267 patients 12 years of age and older with asthma [forced expiratory volume in 1 second (FEV_1) of 40-85% of their predicted normal value] who were symptomatic on short-acting $beta_2$-agonists alone.[11] Baseline characteristics were similar between the treatment groups. Following a 2-week run-in period, patients were randomized to twice daily treatment with *Advair Diskus* 100/50, fluticasone propionate (FP) 100 mcg via *Diskus*, or salmeterol 50 mcg via *Diskus*.

The primary efficacy variables were serial FEV_1 area under the curve (AUC) at treatment week 12 relative to baseline for *Advair Diskus* versus FP, and mean change from baseline in morning (AM) pre-dose FEV_1 at endpoint for *Advair Diskus* versus salmeterol.

At treatment week 12, a significantly greater mean serial FEV_1 AUC relative to treatment day 1 baseline was observed in patients receiving *Advair Diskus* 100/50 compared with those receiving FP or salmeterol (8.4 L-hours, 7.0 L-hours, and 6.2 L-hours, respectively; $P \leq 0.02$).

At endpoint, patients treated with *Advair Diskus* 100/50 experienced a significantly greater improvement in mean AM pre-dose FEV_1 compared with those receiving salmeterol (0.51 L, 0.38 L, respectively; $P = 0.04$). There was no difference between *Advair Diskus* 100/50 and FP with respect to change from baseline in FEV_1 at endpoint. It is important to note that the study was not sufficiently powered to detect a difference between *Advair Diskus* 100/50 and FP for this parameter.

Other secondary efficacy measurements supported the primary efficacy measures in demonstrating efficacy of *Advair Diskus* 100/50 versus FP or salmeterol alone at the same doses as shown in Table 75. *Advair*

Diskus 100/50 resulted in significantly greater improvements in AM PEF, PM PEF, daily asthma symptom scores, and rescue albuterol use compared with both FP and salmeterol alone. In addition, the number of patients withdrawn from the study due to worsening asthma was similar between treatment groups (*Advair Diskus*: 4/88; FP: 2/89; salmeterol: 3/90).

Table 75. Secondary and Other Endpoints (Change from Baseline at Endpoint)

Efficacy Parameter	***Advair Diskus* 100/50 (n = 88)**	**FP 100 mcg (n=89)**	**Salmeterol 50mcg (n = 90)**
Serial FEV_1 AUC at treatment day 1 [weighted average (by time interval)]	0.45 L*	0.24 L	0.31 L
AM PEF	68.1 L/min*†	36.5 L/min	33.0 L/min
PM PEF	51 L/min*†	30.4 L/min	24.4 L/min
Daily asthma symptom scores	-1.3*†	-0.9	-0.9
Rescue albuterol use	-2.8 puffs/day*†	-1.8 puffs/day	-2.6 puffs/day
Nighttime awakenings requiring albuterol	-0.36	-0.27	-0.38

**Advair Diskus* vs. FP, $P < 0.01$.

†*Advair Diskus* vs. salmeterol, $P < 0.04$.

Baseline AM PEF was 348, 358, and 349 L/min for *Advair Diskus*, FP, and salmeterol, respectively.

Baseline PM PEF was 382, 387, and 376 L/min for *Advair Diskus*, FP, and salmeterol, respectively.

Baseline asthma symptom scores were 2.3, 2.4, and 2.4 for *Advair Diskus*, FP, and salmeterol, respectively.

Baseline rescue albuterol use was 4.1, 4.1, and 4.9 puffs/day for *Advair Diskus*, FP, and salmeterol, respectively.

Baseline number of nighttime awakenings requiring albuterol was 0.49, 0.35, and 0.47 for *Advair Diskus*, FP, and salmeterol, respectively.

The overall incidence of adverse events during the 12-week study period was comparable across treatment groups. Candidiasis of the mouth or throat, throat irritation, and headache were the most commonly reported (≥ 3%) drug-related adverse events. No serious drug-related adverse events and no clinically relevant differences in laboratory test results were noted among treatment groups.

Clinical Studies: Advair Diskus versus FP

Advair Diskus 100/50 versus FP 100 mcg

In a 24-week multicenter, randomized, double-blind clinical study, *Advair Diskus* 100/50 twice daily was compared to fluticasone propionate 100 mcg twice daily (via *Diskus*) in 150 patients with persistent asthma treated only with a short-acting $beta_2$-agonist. [12] Patients ≥ 18 years of age were included if they used a short acting bronchodialator at least once per week for asthma symptoms. The primary efficacy endpoint was percentage of symptom-fee days and nights (24-hour period). Secondary endpoints included: morning and evening PEF, asthma symptom scores, albuterol use, episode-free day and nights, exacerbations and adverse events.

Baseline demographics between treatment groups were similar. [12] Patients treated with *Advair Diskus* 100/50 had a significantly higher percentage of symptom-free days and nights (24-hour period) compared to FP with a treatment difference of 15.3%, $P = 0.008$. Improvements in morning and evening PEF, percent of days with no albuterol use, day symptom score, percent episode-free day and nights were also significantly higher in patients receiving *Advair Diskus* (Table 76). No difference in exacerbations was seen between treatment groups. In a sub-analysis of patients with mild asthma (n = 74), patients receiving *Advair Diskus* also had more symptom-free day and nights than patients receiving FP alone ($P = 0.025$). The safety profile of *Advair* was similar to that reported with FP monotherapy.

Table 76. Primary and Secondary Endpoints

Efficacy Parameter	*Advair Diskus* 100/50 n = 78	FP 100 mcg n = 72	*P*-value
% Symptom-free days & nights			
Baseline	20	24	0.008
Change	44	27	
AM PEF (L/min)			
Baseline	380	397	0.0011
Change	56	23	
PM PEF (L/min)			
Baseline	408	418	0.011
Change	40	14	
Day Symptom Score			
Baseline	1.4	1.3	0.0047
Change	-0.9	-0.6	
Night Symptom Score			
Baseline	0.6	0.5	0.27
Change	-0.4	-0.3	
% of Days & Nights With No Albuterol Use			
Baseline	22	25	0.0497
Change	49	38	
Albuterol Use (# episodes day & night)			
Baseline	2.3	2.1	0.14
Change	-1.2	-0.8	
% Episode-free days & nights			
Baseline	15	17	0.015
Change	45	30	

Advair Diskus 100/50 versus FP 250 mcg

A 12-week, randomized, double-blind, parallel-group study by Kotaniemi et al [26] compared *Advair Diskus* 100/50 mcg twice daily and FP 250 mcg twice daily via *Diskus* as first-line therapy in 154 steroid-naïve adult patients with asthma. Compared with FP alone, treatment with *Advair Diskus* 100/50 mcg resulted in significantly greater improvements in patient-measured morning ($P < 0.0001$) and evening PEF ($P = 0.0005$) as well as clinic-measured PEF ($P < 0.02$) and FEV_1 ($P < 0.02$). Both treatments groups resulted in similar improvements in other measures of asthma control, including assessments of symptoms and rescue medication use.

Advair Diskus 250/50 versus FP 250

Advair Diskus 250/50 twice daily was compared with FP 250 mcg twice daily via *Diskus* as initial maintenance therapy in 362 patients with moderate persistent asthma.[213] This 12-week multicenter, randomized, double-blind, parallel group study included patients 12-80 years of age who were previously treated with short-acting $beta_2$-agonists alone. After a 2-week run-in period, patients who met the predetermined asthma severity criteria were randomized to receive *Advair Diskus* 250/50 twice daily or FP 250 mcg twice daily. For the primary endpoint, adjusted mean change in morning PEF over 12 weeks, patients receiving *Advair Diskus* had a significantly higher increases compared with FP (72 L/min vs. 51 L/min; treatment difference 21 L/min [95% CI: 11, 31;$P < 0.001$]). The median percent of symptom-free days increased from 0% at baseline in both groups to 78% and 61% for patients treated with *Advair* and FP, respectively (treatment difference 7% [95% CI: 1, 16;$P = 0.004$). The median percent of symptom-free nights increased from 0% at baseline in both groups to 91% and 75% for patients treated with *Advair* and FP, respectively (treatment difference 5% [95% CI: 1, 12;$P = 0.001$). The median percent of rescue-free days improved from 0% at baseline in both groups to 91% with *Advair* and 73% with FP (treatment difference 6% [95% CI: 2, 13;$P < 0.001$). The median percent of rescue-free nights increased from a baseline of 23% for the *Advair* group and 14% for the FP group to 95% and 84%, respectively (treatment difference 5% [CI 95%: 1, 11;$P < 0.001$). Well controlled asthma was defined as normal lung function, minimal symptoms and rescue albuterol use, no night time awakenings, no exacerbations, no

emergency visits and no side effects leading to withdrawal, and was assessed each week. Patients were considered well controlled if they met all of the criteria on at least 7 of the last 8 weeks. Based on this definition, patients treated with *Advair* were more controlled compared with those treated with FP, OR 1.83 (95% CI 1.2, 2.9; $P = 0.008$).

The mean exacerbation rate per year was similar between treatment groups (*Advair* 0.1; FP 0.2). Both treatments were well tolerated with fewer adverse events reported with *Advair* (19%) compared with FP (26%). The most commonly reported adverse events included acute bronchitis (*Advair* 2%; FP 3%) and headache (*Advair* 3%; FP 3%).

8.4 Use of *Advair* HFA in Children for the Treatment of Asthma

A 12-week, multi-center, randomized, double-blind, double-dummy, parallel group study compared *Advair Diskus* 100/50 one inhalation twice daily and *Advair HFA* 50/25 (dose expressed as ex-valve) two inhalations twice daily to demonstrate clinical equivalence between the two formulations in children with asthma.[214] The study included 428 pediatric patients 4-11 years of age who were receiving an ICS (beclomethasone, budesonide, or flunisolide ≤500 mcg/day or fluticasone propionate ≤200 mcg/day) for at least 4 weeks before the run-in period. Additional inclusion criteria were mean morning PEF 50-85% of predicted post-albuterol, and a daytime plus nighttime symptom score ≥1 on 4 of the last 7 days of the run-in. The primary efficacy endpoint was the mean improvement from baseline in morning pre-dose PEF over the 12-week treatment period. Demographic characteristics were similar between groups.

For the primary endpoint, mean AM PEF improvement from baseline was 37.7 L/min and 38.6 L/min in the groups treated with *Advair Diskus* and *Advair HFA*, respectively. The mean treatment difference was -0.9 L/min which was within the predefined criteria for equivalence. The overall adjusted mean increase from baseline in percent of predicted AM PEF over weeks 1-12 was 17.7% in the group treated with *Advair Diskus* and 17.4% in the *Advair HFA* group.

Table 77. Secondary Endpoints

	Advair Diskus* (n=160)		***Advair HFA* (n=168)***	
	Baseline	Weeks 1-12	Baseline	Weeks 1-12
Mean PM PEF (L/min)	233.5	262.7	226.3	263.2
Mean FEV_1 (L)	1.62	1.78	1.62	1.83
Week 12 Daytime Symptom Score (mean)	1.0	0.4	1.0	0.4
Week 12 Night-time Symptom Score (mean)	0.6	0.2	0.6	0.2
Symptom-free days (median %)	29	85	29	86
Symptom-free nights (median %)	50	92	50	92.5
Rescue-free days (median %)	86	99	86	99
Rescue-free nights (median %)	100	100	100	100
*Per protocol population (excluded major protocol violators)				

Seven patients in each group experienced an exacerbation during the study period (1 patient experienced 2 exacerbations). One exacerbation was considered severe (deterioration requiring hospitalization). Adverse events considered to be related to study medication were experienced by 2% of subjects in each treatment group. Urinary cortisol changes (creatinine corrected) were not significantly different between the groups.

The safety of *Advair HFA* was compared to that of fluticasone propionate (FP) HFA inhalation aerosol in a multicenter, randomized, double-blind, double-dummy, parallel group study in children with persistent asthma ages 4 to 11 years.[67] Inclusion criteria included a morning pre-albuterol forced expiratory volume in one second (FEV_1) ≥60% of predicted (for children 6-11 years) or a peak expiratory flow (PEF) ≥60% of predicted (for children 4 and 5 years) with evidence of reversible airway disease. Patients were stratified by age and spacer use and randomized to receive either *Advair HFA* 50/25 (ex-valve strength) two inhalations twice daily or FP 50 mcg (ex-valve strength) two inhalations twice daily. The use of an AeroChamber Plus® spacer was allowed during the study for patients who were unable to coordinate a

metered dose inhaler alone. A summary of patient baseline characteristics appears in Table 78.The median days of exposure to study medication was 84 for both treatment groups.

Table 78. Baseline Characteristics

	***Advair HFA* (n=173)**	**FP (n=177)**
Male	62%	60%
Caucasian	67%	64%
Age 4 to 5 years Age 6 to 11 years	21% 79%	23% 77%
Spacer Use	78%	77%
Mean PEF % Predicted, 4-5 years	94.6	94.9
Mean FEV_1 % Predicted, 6-11 years	87.9	86.9

A total of 57% of patients treated with *Advair HFA* and 58% of patients treated with FP experienced at least one adverse event. The incidence of adverse events was generally similar between treatment groups except for pharyngitis and pyrexia (Table 79). The incidence of oropharyngeal candidiasis was low. Two patients treated with *Advair HFA* (bronchitis and cough) and one patient treated with FP (headache) discontinued the study due to adverse events.

Table 79. Most Common Adverse Events (≥5%) in Either Treatment Group

Adverse Event	***Advair HFA***	**FP**
Headache	15%	14%
Nasopharyngitis	9%	12%
Pyrexia	5%	9%
Upper Respiratory Tract Infection	6%	7%
Pharyngitis	2%	7%
Cough	5%	4%
Rhinitis	5%	3%

Hematology and chemistry abnormalities occurred at a low incidence, were generally minor in nature, and were similar between treatment groups.

One patient in the Advair HFA and 3 patients in the FP group reported an asthma exacerbation during the study. Of these, one patient treated with Advair and two patients treated with FP were withdrawn from the study due to the exacerbation. No patients were hospitalized for an asthma exacerbation during treatment.

This study was not designed or powered to compare efficacy between treatment groups. However, information regarding lung function, asthma symptoms and albuterol use was collected. For patients 6 to 11 years of age, mean change from baseline in morning pre-dose FEV_1 was 0.23 L in patients taking *Advair HFA* and 0.17 L for patients taking FP . For patients 4 and 5 years, mean change from baseline in morning PEF was 25.3 L/min for patients treated with *Advair HFA* and 23.3 L/min for patients treated with FP. Improvements from baseline in the percentage of symptom-free days (32%-35%) and albuterol-free days (30%-33%) were seen in both treatment groups and were comparable between treatments.

9. EVIDENCE TABLES

9.1 Evidence Tables: *Advair Diskus* Compared with Individual Components in Asthma

Table 80. - See Appendix

9.2 Evidence Tables: *Advair Diskus* Compared with Individual Components in Children with Asthma

Table 81. - See Appendix

9.3 Evidence Tables: *Advair* HFA Compared with Individual Components in Adults and Adolescent Patients with Asthma

Table 82. - See Appendix

9.4 Evidence Tables: *Advair* Compared with Budesonide Formoterol Combination in Asthma

Table 83. - See Appendix

9.5 Evidence Tables: *Advair Diskus* 250/50 Compared with Individual Components in Patients with COPD

Table 84. - See Appendix

9.6 Evidence Tables: *Advair Diskus* 500/50 Compared with Individual Components in Patients with COPD

Table 85. - See Appendix

10. OUTCOME AND ECONOMIC EVALUATIONS

10.1 Pharmacoeconomic Evaluations of *Advair* in the Treatment of Asthma

Advair Diskus vs. Fluticasone Propionate (FP) or FP plus Salmeterol

O'Connor et al conducted a retrospective cohort study of three commercial health plans and one state Medicaid plan to evaluate the incidence of asthma-related hospitalizations and emergency department (ED) visits in patients receiving *Advair Diskus*, FP plus salmeterol in separate devices, or FP. [38] The study included patients with a diagnosis of asthma, who were 15 years and older and had received a prescription for one of these medications between April and September 2001. Patients also had to have a prescription filled for a short-acting beta-agonist within the previous 12 months and have continuous health plan coverage during the study period, April 2000 to December 2002.

A total of 2,414 patients were included in the study (*Advair Diskus* n=1013; FP plus salmeterol n=271; FP n=1130). The incidence of asthma-related hospitalizations and ED visits among patients receiving *Advair Diskus*, FP plus salmeterol, and FP were 3%, 8%, and 4%, respectively. Patients receiving *Advair* had a significantly lower rate of these events compared with FP plus salmeterol [OR 0.69; 95% CI (0.51, 0.95)] and FP alone [OR 0.75; 95% CI (0.61, 0.93)].

Advair Diskus vs. FP Alone

A retrospective, observational study of a large health insurance claims database compared the risk of asthma-related exacerbations (ED and inpatient visits), and all-cause and asthma-related intubations among patients receiving *Advair Diskus* or FP alone.[222] Patients were included if they were ≥12 years of age, had a diagnosis of asthma and had a prescription claim for either *Advair Diskus* or FP between 1/1/2001 and 4/30/2005 (index date). Patients were required to have continuous enrollment 12 months prior to and 60 days after the index date. Patients were excluded if they had used an asthma controller medication prior to the index date, a diagnosis of COPD or were switched to another controller medication within 60 days of the index date. Multivariate analysis of events was conducted using logistic regression.

A total of 58,270 subjects met the inclusion criteria: 73% (42,466) were treated with *Advair Diskus* and 27% (15,804) with FP alone. The mean age was about 37 years, and approximately 62% of the subjects were female.

Patients treated with *Advair* had significantly decreased risk of an asthma-related ED and inpatient visit and of an asthma-related ED visit; see Table 86. There was a non-significant risk reduction for an asthma-related inpatient visit. The predicted annual adjusted rate (per 100 person-years) of all-cause intubations was 0.19 in the *Advair* subjects and 0.24 in the FP subjects ($P<0.01$), while the predicted annual adjusted asthma-related intubation rate was 0.07 for both the *Advair* and FP subjects.

Table 86. Risk of Post-Index Events with *Advair Diskus* versus Fluticasone Propionate Alone.

	Adjusted Odds Ratio, *Advair* vs. FP	95% Confidence Interval
Asthma-related ED or inpatient visit	0.80	(0.73-0.88)
Asthma-related ED visit	0.79	(0.72-0.87)
Asthma-related inpatient visit	0.80	(0.62-1.02)

Advair Diskus vs. ICS plus Montelukast or ICS plus Salmeterol

A retrospective, observational, cohort study based on medical and pharmacy claims from a large health insurance database compared healthcare utilization and cost in patients who switched from an inhaled corticosteroid (ICS) to *Advair Diskus* (n=1287) or initiated add-on treatment with either salmeterol (n=562) or montelukast (n=420).[40] Patients greater than 5 years of age with 24 months of continuous enrollment were included if they had a diagnosis of asthma (ICD-9-CM=493.xx), ≥1 prescription claim for ICS in the 12-month pre-index period, and at least 2 prescriptions claims for *Advair Diskus*, ICS + salmeterol, or ICS + montelukast (index claim plus one additional claim in post-index period). The index date was defined as the first prescription for *Advair Diskus*, montelukast or salmeterol. Patients were excluded if they had a diagnosis of COPD or respiratory cancer, or pre-index claim for a long-acting $beta_2$-agonist, leukotriene receptor antagonist, or theophylline. Outcomes were compared across all three cohorts after adjusting for pre-index characteristics.

Economic Analyses from Clinical Trials

<u>*Advair Diskus* vs. FP plus Montelukast</u>

O'Connor et al conducted an economic analysis to compare the cost-effectiveness of adding either inhaled salmeterol or oral montelukast to inhaled FP in patients ≥15 years of age with persistent asthma who were symptomatic despite inhaled corticosteroid therapy. [41] The analysis was based upon a 12-week, randomized, double-blind, double-dummy, parallel-group study which compared *Advair Diskus* 100/50 twice daily (n=222) and oral montelukast 10 mg once daily plus inhaled FP 100 mcg twice daily (n=225). Effectiveness was defined as the proportion of patients who achieved a ≥12% increase in FEV_1 from baseline. The direct costs used in the analysis included the costs of study drugs, hospital visits, emergency room visits, unscheduled physician visits, rescue medication use, and management of drug-related adverse events.

A significantly higher proportion of patients were 'effectively' treated with *Advair Diskus* 100/50 versus montelukast plus FP (54% vs. 32%; $P<0.001$). In addition, significantly fewer patients treated with *Advair Diskus* 100/50 experienced an exacerbation compared with the montelukast plus FP group (2% vs. 6%; $P<0.031$). The total daily cost per patient was $3.64 in the group treated with *Advair Diskus* 100/50 compared with $4.64 in the montelukast plus FP group ($P<0.001$). Consequently, the cost-effectiveness ratios were $6.77 for *Advair Diskus* 100/50 and $14.59 for montelukast plus FP.

<u>*Advair Diskus* vs. Montelukast</u>

An economic analysis compared the cost-effectiveness of initiating therapy with either *Advair Diskus* 100/50 or oral montelukast in patients whose asthma were inadequately controlled with short-acting $beta_2$-agonists therapy alone. [42] The analysis was based upon a 12-week, randomized, double-blind, double-dummy, parallel-group study that compared *Advair Diskus* 100/50 twice daily (n=211) and montelukast 10 mg once daily (n=212). [27] Patients were ≥15 years of age and had a baseline FEV_1 of 50%-80% of predicted. Effectiveness parameters used in the analysis included the proportion of patients in each treatment group achieving an improvement of at least 12% from baseline in FEV_1 and the percent of symptom-free days achieved during the study. The direct costs included the cost of study drugs, emergency room visits, unscheduled physician visits and hospitalizations related to asthma exacerbations, treatment costs for drug-related adverse events, and rescue medication.

Treatment with *Advair Diskus* 100/50 resulted in a significantly higher proportion of patients who achieved a ≥12% improvement in FEV_1 compared with montelukast (71% versus 39%, $P<0.001$). In addition, patients treated with *Advair Diskus* 100/50 experienced a significantly greater percentage of symptom-free days compared with montelukast (46.8% vs. 21.5%, $P<0.001$). Mean total cost per patient (drug and non-drug) was significantly higher for *Advair Diskus* 100/50 compared with montelukast ($3.55/day versus $3.12/day, $P<0.001$). Treatment drug costs were significantly higher for *Advair Diskus* 100/50 ($3.37/day versus $2.68/day) while non-drug costs (such as physician visits and rescue medication) were significantly higher for the montelukast group ($0.44/day versus $0.18/day). The mean daily costs per successfully treated patient (i.e., patient achieving a ≥12% improvement in FEV_1) were lower in the group treated with *Advair Diskus* 100/50 ($5.03/day; 95% confidence interval [CI]: $4.61, $5.50) compared with montelukast ($8.25/day; 95% CI: $6.98, $9.93). The mean daily cost per symptom-free day was also lower in the group treated with *Advair Diskus* 100/50 ($7.63/day; 95% CI: $6.90, $8.50) compared with

montelukast ($14.89/day; 95% CI: $12.36, $17.98). Incremental cost efficacy ratios demonstrated that the additional costs to achieve these beneficial effects were minimal. The cost per day for each additional person achieving a ≥12% improvement in FEV_1 using *Advair Diskus* 100/50 was $1.33 (95% CI: $0.80, $2.02). Similarly, the cost per day for an additional symptom-free day using *Advair Diskus* 100/50 was $1.69 (95% CI: $1.01, $2.48). Rutten-van Molken et al reported that the cost per symptom-free day of $5.00 (1989 dollars) was regarded as an acceptable amount to pay for a day without symptoms. [43]

An economic analysis was conducted on a study of identical design comparing *Advair Diskus* 100/50 (n=213) and montelukast 10 mg (n=213) as initial maintenance therapy for asthma.[44] [29,195] A significantly higher proportion of patients treated with *Advair Diskus* 100/50 compared with montelukast achieved a ≥12% improvement in FEV_1 (73% versus 46%, P<0.001). Additionally, patients treated with *Advair Diskus* 100/50 experienced a significantly greater percentage of symptom-free days compared with montelukast (44% versus 26%, *P*<0.001). Based on an incremental cost-effectiveness ratio, the average extra cost per day for an additional symptom-free day was $2.87 with *Advair Diskus* than with montelukast. The average extra cost per day to achieve an increase in FEV_1 of ≥12% with *Advair Diskus* than with montelukast was $1.79. An incremental cost-effectiveness ratio of ≤ $9.95 per day (2003 dollars) was considered a reasonable price to pay for increased value. Consequently, treatment with *Advair Diskus* was found to be more cost-effective than montelukast in the initial maintenance therapy of persistent asthma.

Pooled Analysis: *Advair Diskus* vs. Montelukast or FP

O'Connor et al [223] reported the results of a pooled analysis of four published, randomized, double-blind, double-dummy studies comparing *Advair Diskus* with montelukast [29] [27] and montelukast with FP [224] [225] in patients previously uncontrolled on albuterol alone. A total of 1910 patients were included in the analysis. Baseline demographics of all groups were similar. Compared with patients treated with *Advair Diskus*, patients treated with FP or montelukast had a 2.6 times and 3.6 times greater risk, respectively, of having an asthma exacerbation within 12 weeks of starting therapy. Exacerbation costs per treated patient were $0.41 for *Advair Diskus*, $4.60 for FP, and $7.57 for montelukast. Additionally, mean daily costs per patient exacerbation was $29 for *Advair Diskus* compared with $128 for FP and $154 for montelukast.

Pediatric Observational Studies

Advair Diskus vs. FP plus Montelukast

A retrospective, observational study compared healthcare utilization and costs with *Advair Diskus* and FP plus montelukast in children 4-17 years of age previously receiving an ICS.[226] Medical and pharmacy data was obtained from a large database of 75 managed care plans across the US. Patients were included if they had a diagnosis of asthma (ICD-9-CM-493.xx) and a prescription claim for either *Advair Diskus* or FP plus montelukast (filled within a 60 day period) between January 1, 2001, and December 31, 2003. Patients also had to have a prescription claim for an ICS in the 12-month pre-index period, and have continuous enrollment 12 months prior to and post the index date. Patients were excluded if they switched or augmented asthma therapy in the 60 days following the index claim, used a non-ICS controller in the 12-month pre-index period, had a prescription claim for omalizumab, *Advair Diskus* 500/50 or high dose FP 220 during the 12-month pre- or post-index period, or had a diagnosis of cystic fibrosis, COPD, bronchopulmonary dysplasia or respiratory distress syndrome.

After patients were matched based on propensity scores, 186 patients were included in each treatment group. Baseline characteristics were comparable between cohorts except for a greater number of ICS claims in the 12-month pre-index period in the FP + montelukast cohort compared with *Advair Diskus* (3.3 vs. 1.9 claims, *P*=0.0001). Three outcomes were evaluated: (1) asthma-related hospitalizations or emergency room visits only, (2) treatment failure, defined as asthma-related hospitalizations/emergency room visits or any switching/augmentation of the index asthma therapy, and (3) asthma-related costs. After adjusting for baseline differences, patients treated with the FP + montelukast were nearly 90% more likely to experience treatment failure when compared to children who received *Advair* (Odds Ratio =1.88; 95% CI: 1.05-3.37). The FP + montelukast cohort was at a 3.6-fold greater risk of a hospitalization or ED event compared to those treated with *Advair* (OR=3.65; 95% CI: 1.32-10.05). In addition, children treated with FP + montelukast incurred higher asthma-related costs than those treated with *Advair*. Smearing methods were applied to obtain estimates of the magnitude of the treatment effect and revealed mean costs of $1,202 (SD=$570) with *Advair* versus $2,253 (SD=$1,068) with FP + montelukast. After

accounting for potential confounders, asthma-related treatment costs were nearly 2-fold higher with FP + montelukast compared with *Advair* ($P<0.0001$).

10.2 Compliance/Adherence with *Advair Diskus* in Asthma

Studies Assessing Compliance with Advair Diskus

US Studies– Adults and Adolescents

Study 1

A retrospective study was conducted using medical and pharmacy claims data to assess compliance with *Advair Diskus* in a large managed care organization. [33] The study included patients ≥12 years of age with asthma (ICD-9 493.XX) with an index claim for controller therapy from April 2001 through July 2001. Pharmacy utilization was examined in the 12 months prior and 12 months following a pharmacy claim for one of the following asthma medications: *Advair Diskus* (n = 563), concurrent fluticasone propionate (FP) and salmeterol via separate inhalers (FP + SAL; n = 224), FP plus montelukast (n = 75), FP alone (n = 798), and montelukast alone (n = 776). Patients with chronic obstructive pulmonary disease (COPD), cystic fibrosis, or high-dose FP use (FP 220 mcg or *Advair Diskus* 500/50) were excluded from the study. Refill rates were compared in the 12-month post-index period as a measure of compliance.

The refill rates for all treatment groups are displayed in Table 87. The refill rate for *Advair Diskus* was significantly higher compared with the refill rates of FP in the groups prescribed concurrent FP plus salmeterol, FP plus montelukast, or FP alone. These results suggest that the use of *Advair Diskus* may increase inhaled corticosteroid (ICS) refill persistence. The refill rate for *Advair Diskus* was similar to single controller use of montelukast.

Table 87. Mean No. of Prescription Claims per Patient in the 12-Month Post-Index Period

	Claims
Advair Diskus (n = 563)	4.06†
FP + SAL* (n = 224)	2.35
FP + montelukast* (n = 75)	1.83
FP alone (n = 798)	2.27
Montelukast alone (n = 776)	4.51
*Claims for FP portion †$P < 0.05$ versus the refill rate of FP in the FP + SAL, FP + montelukast, and FP alone groups	

Furthermore, only the group treated with *Advair Diskus* had a decrease in the adjusted mean number of post-index claims for short-acting beta-agonists compared with pre-index values (Table 88).

Table 88. Mean No. of SABA Prescription Claims per Patient

Cohort	**Claims (pre-index)**	**Claims (post-index)**
Advair Diskus (n = 563)	1.87	1.61*
FP + SAL (n = 224)	2.11	2.28
FP + montelukast (n = 75)	1.77	2.53
FP alone (n = 798)	1.54	1.97
Montelukast alone (n = 776)	1.64	1.97
*$P < 0.05$ versus FP + SAL or FP + montelukast groups		

Study 2

In a second, similarly designed retrospective analysis, medical and pharmacy claims from three commercial health plans and one Medicaid plan were evaluated to assess adherence with *Advair Diskus* compared with concurrent FP + SAL, FP + montelukast, FP alone, and montelukast alone. [34] Nearly 8 million members were covered by the three commercial healthplans, while the Medicaid plan covered more than 1.6 million recipients. Patients included were at least 12 years old, with a medical claim for asthma and a prescription claim for a short-acting beta-agonist sometime in the 12 months preceding the index prescription claim. In addition, subjects were required to have continuous enrollment in their respective healthplan for 12 months before and 12 months following the index event, which was defined as a pharmacy claim for one

of the drug regimens listed above during the index period (April-Sept 2001). Patients with COPD and cystic fibrosis were excluded from the study as were those who had received an inhaled corticosteroid, long-acting beta$_2$-agonist or leukotriene modifier in the 12 months proceeding the index period. Refill rates during the 12-month post-index period were compared to assess adherence (Table 89).

Table 89. Mean No. of Prescription Claims per Patient in the 12-Month Post-Index Period

	Claims
Advair Diskus (n = 996)	3.98†
FP + SAL* (n = 259)	2.36
FP + montelukast* (n = 101)	2.15
FP alone (n = 1254)	2.29
Montelukast (n = 893)	4.33
†$P < 0.05$ versus the refill rates of FP in the FP + SAL, FP + montelukast, and FP alone groups *Claims for FP portion	

These data demonstrate that the cohort treated with *Advair Diskus* had significantly higher refill rates compared with the FP + SAL, FP + montelukast or FP alone groups. The refill rates were similar between the groups treated with *Advair Diskus* and montelukast. The mean number of prescriptions for short-acting beta-agonists in the 12-month post-index period is summarized in Table 90.

Table 90. Mean No. of SABA Prescription Claims per Patient in the 12-Month Post-Index Period

	Claims
Advair Diskus (n = 996)	2.34*
FP + SAL (n = 259)	2.59
FP + montelukast (n = 101)	2.55
FP alone (n = 1254)	2.62
Montelukast (n = 893)	2.79
*$P < 0.0001$ compared to montelukast	

Study 3

A retrospective observational study was conducted using medical and pharmacy claims data over a 5-year period (August 1998-August 2003) from a large health insurance claims database to determine refill persistence in patients stepped-up from an ICS to combination therapy with *Advair Diskus* (n = 1287), ICS + SAL (n = 562), or ICS + montelukast (n = 420).[35] Patients included were ≥5 years old, diagnosed with asthma and had at least one prescription for an ICS in the 12 months proceeding the index date. The index date was the time patients switched to *Advair Diskus*, ICS + salmeterol or ICS + montelukast.

Compared to patients who added on salmeterol or montelukast, patients switched to *Advair Diskus* had a significantly greater mean ICS refill rate ($P < 0.001$) and mean medication possession ratio (MPR; $P < 0.001$) in the 12 months post-index (Figure 34, Figure 35). MPR is the number of days in the interval with drug supply divided by the number of days in the interval.

Figure 34. Mean ICS Refill Rate in the 12 Months Post-Index

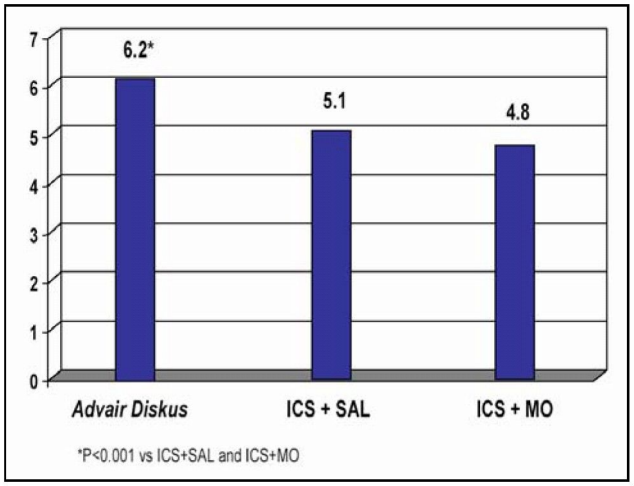
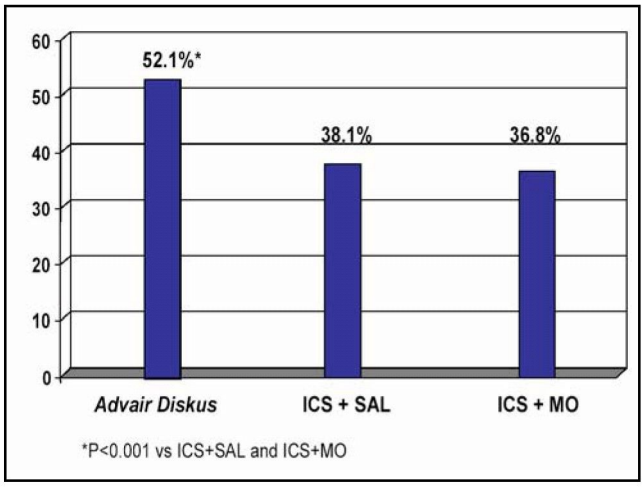


Figure 35. Mean ICS MPR in the 12 Months Post-Index



US Studies - Pediatric Patients

A retrospective, observational study evaluated refill persistence of asthma medications among 4,946 pediatric patients (4-17 years) in a managed care organization.[36] Patients included were diagnosed with asthma (ICD-9 493) between 1/1/2001 – 5/31/2002 and had received an index prescription for one of the following: *Advair Diskus* (n = 1168), FP alone (n = 2473), concurrent ICS and salmeterol via separate inhalers (ICS + SAL; n = 296), or ICS plus montelukast (n = 1009). Patients were required to belong to one of the treatment groups for the first 60 days. Prior to the index prescription patients had not received asthma controller medication in the previous 6 months. Patients were excluded if they had a diagnosis of cystic fibrosis, COPD, bronchopulmonary dysplasia or respiratory distress syndrome. Numbers of ICS prescription refill claims were monitored for the following 12 months.

For patients who filled more than 1 prescription, the mean refill rate over 12 months for *Advair Diskus* was significantly higher than the other ICS cohorts (Table 91).

Table 91. Mean No. of Prescription Claims per Patient in the 12-Month Post-Index Period for Patients with >1 Prescription

	Claims*
Advair Diskus	4.48†
FP alone	3.39
ICS + SAL	3.61
ICS + MON	3.92
*Claims for ICS portion †$P < 0.05$ vs. refill rates for FP alone, ICS+SAL, and ICS+MON	

Compliance with Advair Diskus and Clinical Outcomes

A retrospective longitudinal analysis using linked medical and pharmacy claims from a managed care database of more than 70 US health plans evaluated adherence with *Advair Diskus* and clinical outcomes in asthma patients.[37] Patients included in the analysis were 12 years and older, had a diagnosis of asthma and had filled two or more prescriptions for *Advair Diskus* between January 1, 2000 and December 31, 2004. Patients over 65 years of age who were not enrolled in Medicare risk-sharing plans, those with diagnoses of COPD, or with pharmacy claims for ipratropium were excluded. Patients were also excluded if they had less than 12 months of complete claims data prior to their index date (first *Advair* prescription) or less 12 months of follow-up.

Follow-up time was defined as the time from the index date to disenrollment, discontinuation of *Advair Diskus* (>180 days without supply), receipt of a different controller, or 24 months past the index date which ever came first. Adherence to *Advair Diskus* was assessed quarterly based on the medication possession ratio (MPR). MPR was calculated as the proportion of days during the quarter for which the patient had supply of *Advair Diskus* on hand. Clinical outcomes evaluated included asthma-related emergency department (ED) visits or hospitalizations and were identified based on primary diagnosis codes.

The study included 12,930 patients with a mean age of 40 years, and a mean follow-up of 20 months. The mean quarterly MPR for *Advair Diskus* was 51% and the mean quarterly incidence of asthma-related ED visits/hospitalizations was 0.8%. After controlling for baseline demographics and disease characteristics, the risk of an asthma-related ED visit or hospitalization was reduced as adherence to *Advair Diskus* increased (Table 92). The risk reduction was greatest at the higher adherence levels. For every 25% increase in MPR, there was an associated 11% reduction in asthma-related ED visits or hospitalizations.

Table 92. Adherence to *Advair Diskus* and Associated Reduction in ED Visits and Hospitalizations[37]

***Advair Diskus* MPR %**	**Adjusted Odds Ratio (CI)**	**Odds Reduction**
<25	Referent	-
25 to <50	0.79 (0.64-0.99)	21%
50 to <75	0.74 (0.59-0.93)	26%
75+	0.68 (0.54-0.86)	32%
Every 25% Increase	0.89 (0.83-0.96)	11%
MPR = Medication possession ratio		

10.3 Effect of *Advair Diskus* on Emergency Room Visits and Hospitalizations in COPD

Study 1: Managed Care Plans Database

Medical and pharmacy claims from a large, managed care database (Integrated HealthCare Information Services, which included more than 30 managed care plans and 33 million patients) were reviewed to identify patients receiving initial therapy with *Advair Diskus*, salmeterol, an inhaled corticosteroid (ICS), ipratropium, or ipratropium/albuterol for COPD.[55,58] The index date (first pharmacy claim) occurred between January 2001 and August 2003. Patients ≥ 40 years of age with a primary or secondary diagnosis for COPD (International Classification of Diseases 9th Revision, Clinical Modification [ICD-9-CM] diagnosis and procedure codes [ICD-9-CM 490.xx, 491.xx, 492.xx, 496.xx]) within 1 year of the index date were included in the analysis and subanalyses. Patients with ≥ 1 pharmacy claim for *Advair Diskus*, salmeterol, ICS, ipratropium, or ipratropium plus albuterol between January 2001-August 2003 were included. Continuous enrollment in the plan for 12 months before and 6 or 12 months after the

index date was required. Patients were excluded if they received any COPD medication other than oral corticosteroids, short-acting β_2-agonists, or theophylline in the previous 12 months of the index date or any other COPD medication 60 days following the index date. A Cox proportional hazard analysis was conducted to evaluate time to first all-cause and COPD-related hospitalization/ED visit, and multivariate models adjusted for age, gender, co-morbid conditions, number of prescriptions for respiratory medications and all other medications in the pre-index period, and pre-index hospitalizations and ED visits.

A total of 14, 368 patients were included in the analysis.[58] Patients treated with *Advair Diskus* had a 28% and 52% reduction ($P < 0.05$) in all-cause and COPD-related combined hospitalizations/ED visits risk, respectively, compared with ipratropium (Table 93). Patients in the groups receiving ICS or salmeterol also had significant reductions in the risk of all-cause (23% and 21%, respectively) and COPD-related hospitalizations/ED visit risk (36% and 34%, respectively) compared with ipratropium. Ipratropium/albuterol did not show significant reductions in either endpoint compared with ipratropium alone.

Table 93. Adjusted Risk of All-Cause & COPD-Related Hospitalizations and Emergency Department Visits in Patients with COPD in Managed Care Plans[58]

N=14,368		***Advair Diskus* (any dose) (n=3819)**	**ICS (n=3940)**	**SAL (n=1099)**	**IP/ALB (n=3388)**	**IP (n=2122)**
All-Cause HR (95% CI)	Hospitalizations	0.756 (0.681-0.839)	0.716 (0.646-0.794)	0.782 (0.681-0.899)	0.975 (0.889-1.068)	1 (reference group)
	ED Visits	0.711 (0.651-0.776)	0.792 (0.728-0.862)	0.795 (0.708-0.892)	0.959 (0.885-1.040)	1 (reference group)
	Hospitalizations/ED visits	0.721 (0.665-0.782)	0.772 (0.713-0.835)	0.790 (0.709-0.879)	0.949 (0.881-1.023)	1 (reference group)
COPD-Related HR (95% CI)	Hospitalizations	0.460 (0.329-0.642)	0.572 (0.426-0.768)	0.521 (0.336-0.809)	0.897 (0.705-1.143)	1 (reference group)
	ED Visits	0.456 (0.369-0.563)	0.606 (0.504-0.730)	0.637 (0.492-0.825)	0.979 (0.838-1.144)	1 (reference group)
	Hospitalizations/ED visits	0.480 (0.394-0.585)	0.638 (0.536-0.760)	0.663 (0.520-0.845)	0.970 (0.837-1.124)	1 (reference group)

CI=confidence interval; COPD=chronic obstructive pulmonary disease; ED=emergency department; HR=hazard ratio; ICS=inhaled corticosteroids; IP=ipratropium; IP/ALB=ipratropium and albuterol combination product; N/n = number; SAL=salmeterol

Subanalysis of Patients with COPD and Without Asthma: *Advair Diskus* 250/50

A subanalysis was conducted in patients with COPD and without asthma who were taking *Advair Diskus* 250/50.[55] The use of *Advair Diskus* 250/50 was associated with a 28% lower risk of all-cause hospitalization/ED visits and a 44% lower risk of COPD-related events compared with ipratropium alone ($P < 0.05$).

Table 94. Adjusted Risk of All-Cause & COPD-Related Hospitalizations and Emergency Department Visits in Patients with COPD and without Asthma[58]

		Advair Diskus 250/50	ICS	SAL	IP/ALB	IP
All-Cause HR (95% CI)	Hospitalizations	0.760 (0.647-0.891)	0.743 (0.656-0.841)	0.796 (0.677-0.937)	0.980 (0.884-1.086)	1 (reference group)
	ED Visits	0.720 (0.630-0.823)	0.784 (0.708-0.868)	0.821 (0.716-0.940)	0.947 (0.865-1.037)	1 (reference group)
	Hospitalizations/ED visits	0.719 (0.636-0.813)	0.778 (0.708-0.855)	0.801 (0.706-0.909)	0.938 (0.862-1.021)	1 (reference group)
COPD-Related HR (95% CI)	Hospitalizations	0.576 (0.340-0.978)	0.696 (0.485-0.998)	0.581 (0.345-0.981)	0.960 (0.721-1.277)	1 (reference group)
	ED Visits	0.552 (0.399-0.762)	0.628 (0.500-0.788)	0.761 (0.569-1.018)	1.008 (0.844-1.204)	1 (reference group)
	Hospitalizations/ED visits	0.558 (0.410-0.758)	0.687 (0.556-0.849)	0.771 (0.584-1.016)	1.007 (0.850-1.192)	1 (reference group)

CI=confidence interval; COPD=chronic obstructive pulmonary disease; ED=emergency department; HR=hazard ratio; ICS=inhaled corticosteroids; IP=ipratropium; IP/ALB=ipratropium and albuterol combination product; N/n = number; SAL=salmeterol

Study 2: Healthcare Benefit Plans Database

Medical and pharmacy claims from a large, healthcare benefit plan database (PharMetrics Patient Centric Database, which included more than 70 health plans across the U.S. and over 40 million patients) were reviewed to identify patients receiving initial therapy with *Advair Diskus*, salmeterol, an inhaled corticosteroid (ICS), ipratropium, or ipratropium/albuterol combination for COPD.[56] The index prescription occurred between July 1998 and January 2004. Patients at least 40 years of age with a primary or secondary diagnosis for COPD (ICD-9-CM diagnosis and procedure code 491.xx, 492.xx, or 496.xx) were included in the analysis. Patients had to have at least one outpatient pharmacy claim ("index date") for *Advair Diskus*, salmeterol, ICS, ipratropium, or ipratropium/albuterol combination. Continuous enrollment in the plan for 12 months before and 12 months after the index date was required. Patients who had a claim for another respiratory medication within 60 days of index date, patients enrolled in Medicaid, and patients over 65 years of age not enrolled in Medicare were excluded.

A total of 14,935 patients were included in the analysis. In patients taking *Advair Diskus*, significantly fewer patients (unadjusted) experienced all-cause and COPD-related hospitalization/ED visits compared to patients taking ipratropium or ipratropium/albuterol combination.[56]

Table 95. Percentage of Patients (Unadjusted) with COPD Experiencing Hospitalizations and Emergency Department Visits in Health-Care Benefit Plans[56]

N=14,935	*Advair Diskus* (any dose) n=3548	ICS n=3913	SAL n=1161	IP/ALB n=4544	IP n=1769
All-Cause Hospitalizations/ED visits number (%)	1285 (36.2%)	1414 (36.1%) *P*=0.942	401 (34.5%) *P*=0.301	1789 (39.4%) *P*=0.004	780 (44.1%) *P*<0.0001
COPD-Related Hospitalizations/ED visits number (%)	375 (10.6%)	367 (9.4%) *P*=0.086	109 (9.4%) *P*=0.250	556 (12.2%) *P*=0.020	262 (14.8%) *P*<0.0001

(*P* value vs. *Advair Diskus*)

COPD=chronic obstructive pulmonary disease; ED=emergency department; ICS=inhaled corticosteroids; IP=ipratropium; IP/ALB=ipratropium and albuterol combination product; N/n=number; SAL=salmeterol

Subanalysis of Patients with COPD and Without Asthma: *Advair Diskus* 250/50

A subanalysis was conducted in patients with COPD and without asthma who were taking *Advair Diskus* 250/50.[56] The use of *Advair Diskus* 250/50 was also associated with significantly fewer patients (unadjusted) experiencing all-cause and COPD-related hospitalization/ED visits compared with ipratropium alone. See Table 96.

Table 96. Percentage of COPD Patients (Unadjusted) without Asthma Experiencing Hospitalizations and Emergency Department Visits in Health-Care Benefit Plans[56]

N=9466	*Advair Diskus* 250/50 n=921	ICS n=2398	SAL n=859	IP/ALB n=3863	IP n=1425
All-Cause Hospitalizations/ED visits number (%)	341 (37.0%)	844 (35.2%) *P*=0.325	297 (34.6%) *P*=0.282	1498 (38.8%) *P*=0.326	617 (43.3%) *P*=0.003
COPD-Related Hospitalizations/ED visits number (%)	87 (9.4%)	214 (8.9%) *P*=0.639	86 (10.0%) *P*=0.687	455 (11.8%) *P*=0.045	192 (13.5%) *P*=0.003
(*P* value vs. *Advair Diskus*)					
COPD=chronic obstructive pulmonary disease; ED=emergency department; ICS=inhaled corticosteroids; IP=ipratropium; IP/ALB=ipratropium and albuterol combination product; N/n=number; SAL=salmeterol					

Study 3: Texas Medicaid

Inpatient and outpatient medical plus outpatient pharmacy claims from the Texas Medicaid database (which included about 2.5 million patients) were reviewed to identify patients receiving initial therapy with *Advair Diskus*, salmeterol, an inhaled corticosteroid (ICS), or ipratropium (with or without albuterol) for COPD.[57] Patients 40-64 years of age with a primary or secondary diagnosis for COPD (ICD-9-CM diagnosis and procedure code 491.xx, 492.xx, or 496.xx) were included in the analysis. At least one outpatient pharmacy claims ("index date") for *Advair Diskus*, salmeterol, ICS, or ipratropium between April 2001 - March 2003 was required. Additionally, patients were required to have continuous enrollment in the plan for 12 months before and 12 months after the index date. There were no formulary restrictions or copays for any study medications. A Cox proportional hazard analysis was conducted to evaluate time to first all-cause and COPD-related hospitalization/ED visit across treatment cohorts with adjustment for age, race, sex, presence of co-morbid conditions, pre-index utilization of other respiratory medication, pre-index hospital/ED visits, and pre-index treatment costs.

All-cause and COPD-related hospitalizations/ED risks were significantly lower in patients treated with *Advair Diskus* compared with ipratropium (9.4% and 26.7% lower, respectively). Results are presented in Table 97.[57]

Table 97. Adjusted Risk of Hospitalizations and Emergency Department Visits in Patients with COPD in the Texas Medicaid Database[57]

N=6793	*Advair Diskus* n=1211	ICS n=968	SAL n=401	IP n=4213
All-Cause Hospitalizations/ED visits HR (95% CI)	0.906 (0.844-0.972)	1.105 (1.025-1.192)	1.002 (0.898-1.119)	1 (reference group)
COPD-Related Hospitalizations/ED visits HR (95% CI)	0.733 (0.650-0.826)	0.937 (0.833-1.055)	0.869 (0.728-1.038)	1 (reference group)
CI=confidence interval; COPD=chronic obstructive pulmonary disease; ED=emergency department; HR=hazard ratio; ICS=inhaled corticosteroids; IP=ipratropium; N/n=number; SAL=salmeterol				

10.4 Pharmacoeconomic Evaluations of *Advair Diskus* in COPD

Study 1: Managed Care Plans Database

The cost of treatment associated with different initial maintenance therapies for COPD over one year was evaluated in a retrospective observational analysis of patient-level administrative medical and pharmacy claims from a large managed care database.[55,58] These data represented > 30 plans and covered approximately 33 million patients. Additionally, patients ≥ 40 years of age with a primary or secondary diagnosis for COPD (International Classification of Diseases 9th Revision, Clinical Modification [ICD-9-CM] diagnosis and procedure codes [ICD-9-CM 490.xx, 491.xx, 492.xx, 496.xx]) within 1 year of the index date were included in the analysis and subanalyses. Patients with ≥ 1 pharmacy claim (index date) for a *Advair Diskus*, salmeterol, ICS, ipratropium, or ipratropium plus albuterol between January 2001-August 2003 were included. Continuous enrollment in the plan for 12 months before and 12 months after the index date was required. Patients were excluded if they received any COPD medication other than oral corticosteroids, short-acting β_2-agonists, or theophylline in the previous 12 months of the index date or any other COPD medication 60 days following the index date.

The primary analysis included the impact of COPD maintenance therapies on all-cause and COPD-related costs. Healthcare costs compared across treatment cohorts were estimated by multivariate generalized linear model assuming gamma distribution and log link function. Models were adjusted for baseline differences in demographics, COPD subtype, comorbid conditions, pre-index resource utilization, and pre-index costs.

Patients receiving *Advair Diskus* had significantly lower medical costs in both all-cause and COPD-related services compared with the reference group, ipratropium.[58] Alternatively, those receiving *Advair Diskus* had higher pharmacy costs partly due to increased treatment adherence and refill rates. All-cause total costs were significantly lower for patients receiving *Advair Diskus* compared with ipratropium . COPD-related total costs were similar between *Advair Diskus* and ipratropium cohorts. Results are presented in Table 98.

Table 98. Cost Analysis for Initial Maintenance Therapy for COPD in Managed Care Plans[58]

N=9,743		*Advair Diskus* (any dose) (n=2254)	Salmeterol (n=842)	Inhaled Corticosteroids (n=2903)	Ipratropium plus Albuterol (n=2258)	Ipratropium (n=1486)
Adjusted Mean Annual Medical Costs ($US)	All-Cause	8662	9962	9116	10,382	11,826
	COPD-Related	1264	1274	1288	1454	1697
Adjusted Mean Annual Difference Medical Costs ($US)	All-Cause	-3164*	-1864*	-2710*	-1444*	REF
	COPD-Related	-432*	-423*	-409*	-242*	REF
Adjusted Mean Annual Pharmacy Costs ($US)	All-Cause	2674	2170	2085	2369	2436
	COPD-Related	587	362	357	311	349
Adjusted Mean Annual Difference Pharmacy Costs ($US)	All-Cause	237*	-266*	-352*	-68	REF
	COPD-Related	238*	12*	7*	-38*	REF
Adjusted Mean Annual Total Costs ($US)	All-Cause	11,282	12,135	11,229	12,843	14,278
	COPD-Related	1991	1667	1655	1724	2015
Adjusted Mean Annual Difference Total Costs ($US)	All-Cause	-2996*	-2143*	-3049*	-1435*	REF
	COPD-Related	-24	-347*	-359*	-290*	REF

*$P<0.05$ vs. ipratropium; REF=Reference

Subanalysis of Patients with COPD and Without Asthma: *Advair Diskus* 250/50

An analysis for patients taking *Advair Diskus* 250/50 without an asthma diagnosis was conducted to examine whether observed treatment effects were modified by the asthma diagnosis.[55] Treatment with *Advair Diskus* 250/50 in resulted in significantly lower all-cause medical and all-cause total costs compared with ipratropium. Cost difference results from this analysis are presented in Table 99.

Table 99. Adjusted Cost Differences Analysis for Initial Maintenance Therapy for COPD Patients Without an Asthma Diagnosis[55]

N=5,981		*Advair Diskus* 250/50	Salmeterol	Inhaled Corticosteroids	Ipratropium plus Albuterol	Ipratropium
Adjusted Mean Annual Difference Medical Costs ($US)	All-Cause	-6420*	-3882	-3728*	-2038	REF
	COPD-Related	-340	-369	-434	-256	REF
Adjusted Mean Annual Difference Pharmacy Costs ($US)	All-Cause	310	-554*	-538*	-144	REF
	COPD-Related	388*	23	-4	-47*	REF
Adjusted Mean Annual Difference Total Costs ($US)	All-Cause	-6025*	-4341	-4238*	-2001	REF
	COPD-Related	167	-331	-470*	-398	REF

*$P<0.05$ vs. ipratropium; REF=Reference

Study 2: Healthcare Benefit Plans Database

The cost of treatment associated with different initial maintenance therapies for patients with COPD over one year was evaluated in a retrospective cohort analysis of patient-level administrative medical and pharmacy claims from a large managed care database (PharMetrics Patient Centric Database).[56] These data represented more than 70 plans and covered approximately 40 million patients.

Patients at least 40 years of age with a primary or secondary diagnosis for COPD (ICD-9-CM) diagnosis and procedure code 491.xx, 492.xx, or 496.xx were included in the analysis. Patients had to have at least one outpatient pharmacy claim ("index date") for *Advair Diskus*, salmeterol, ICS, ipratropium, or ipratropium/albuterol combination between July 1998 - January 2004. Continuous enrollment in the plan for 12 months before and 12 months after the index date was required. Patients who had a claim for another respiratory medication within 60 days of index date, patients enrolled in Medicaid, and patients over 65 years of age not enrolled in Medicare were excluded. The primary analysis was the impact of COPD maintenance therapies on all-cause and COPD-related costs. Healthcare costs compared across treatment cohorts were estimated by multivariate generalized linear model assuming gamma distribution and log link function.

Patients taking *Advair Diskus* had significantly lower COPD-related medical (hospitalization and ED visits) costs compared with those taking ipratropium and ipratropium/albuterol combination, but not compared with those receiving salmeterol or ICS. Alternatively, patients taking *Advair Diskus* had higher total pharmacy costs (both all-cause and COPD-related) partly due to higher treatment adherence and refill rates, and also had higher COPD-related total (medical and pharmacy) compared to all other treatment groups. See Table 100.

Table 100. Cost Analysis for Initial Maintenance Therapy for COPD in Healthcare Plans[56]

N=14,935		*Advair Diskus* (any dose) (n=3548)	Salmeterol (n=1161)	Inhaled Corticosteroids (n=3913)	Ipratropium/ Albuterol Combination (n=4544)	Ipratropium (n=1769)
Adjusted Mean Annual Hospitalization and E.D. Costs ($US)	All-Cause	5021	5372	5339	5875	5931
	COPD-Related	176	266	127	325	278
Adjusted Mean Annual Difference Hospitalization and E.D. Costs ($US)	All-Cause	REF	351	318	854	911
	COPD-Related	REF	91	-49	149*	102*
Adjusted Mean Annual Pharmacy Costs ($US)	All-Cause	2729	2288	2373	2334	2127
	COPD-Related	553	342	294	251	262
Adjusted Mean Annual Difference Pharmacy Costs ($US)	All-Cause	REF	-441*	-356*	-394*	-602*
	COPD-Related	REF	-211*	-259*	-302*	-291*
Adjusted Mean Annual Total Costs ($US)	All-Cause	12,421	11,924	11,783	12,813	12,488
	COPD-Related	1215	975	800	987	978
Adjusted Mean Annual Difference Total Costs ($US)	All-Cause	REF	-497	-638	392	67
	COPD-Related	REF	-240*	-415*	-228*	-237*

*$P<0.05$ vs. *Advair Diskus;* REF=Reference

Subanalysis of Patients with COPD and Without Asthma: *Advair Diskus* 250/50

An analysis of patients taking *Advair Diskus* 250/50 without an asthma diagnosis was conducted to examine whether observed treatment effects were modified by the asthma diagnosis. Total all-cause costs associated with patients receiving *Advair Diskus* 250/50, although higher, were not statistically significant in this population. Total COPD-related costs were significantly greater only in patients receiving *Advair Diskus* 250/50 versus those receiving inhaled corticosteroids. Patients taking *Advair Diskus* 250/50 had significantly lower COPD-related medical (hospitalization and ED visits) costs compared with those taking ipratropium/albuterol combination. Pharmacy costs were similar to those observed in the broader COPD population. Cost difference results from this analysis are presented in Table 101.

Table 101. Adjusted Cost Differences Analysis for Initial Maintenance Therapy for COPD Patients Without an Asthma Diagnosis

N=9,466		*Advair Diskus* 250/50 (n=921)	Salmeterol (n=859)	Inhaled Corticosteroids (n=2398)	Ipratropium plus Albuterol (n=3863)	Ipratropium (n=1425)
Adjusted Mean Annual Difference Hospitalization and E.D. Costs ($US)	All-Cause	REF	-573	6	261	385
	COPD-Related	REF	147	-7	236*	100
Adjusted Mean Annual Difference Pharmacy Costs ($US)	All-Cause	REF	-351	-252	-284*	-435*
	COPD-Related	REF	-168*	-223*	-250*	-239*
Adjusted Mean Annual Difference Total Costs ($US)	All-Cause	REF	-749	-1158	-331	-395
	COPD-Related	REF	-108	-337*	-112	-137

*$P<0.05$ vs. *Advair Diskus* 250/50; REF=Reference

Study 3: Texas Medicaid

The cost of treatment associated with different initial maintenance therapies for patients with COPD over one year was evaluated in a retrospective cohort analysis of patient-level administrative medical and pharmacy claims (N=5582) from the Texas Medicaid database.[57] Patients 40-64 years of age with a primary or secondary diagnosis for COPD (ICD-9-CM diagnosis and procedure code 491.xx, 492.xx, or 496.xx) were included in the analysis. At least one outpatient pharmacy claims ("index date") for *Advair Diskus*, salmeterol, ICS, or ipratropium between April 2001 - March 2003 was required. Additionally, patients were required to have continuous enrollment in the plan for 12 months before and 12 months after the index date. There were no formulary restrictions or copays for any study medications. Healthcare costs were compared across treatment cohorts with adjustment for age, race, sex, presence of co-morbid conditions, pre-index utilization of other respiratory medication, pre-index hospital/ED visits, and pre-index treatment costs.

Patients receiving *Advair Diskus* had significantly lower COPD-related medical (hospitalization, ED visits, and treatment-related) costs compared with ipratropium. Alternatively, patients receiving *Advair Diskus* had significantly higher total pharmacy costs (both all-cause and COPD-related) partly due to higher treatment adherence and refill rates. See Table 102.

Table 102. Cost Analysis for Initial Maintenance Therapy for COPD in the Texas Medicaid Database[57]

N=5582		*Advair Diskus* (any dose) (n=1211)	Salmeterol (n=401)	Inhaled Corticosteroids (n=968)	Ipratropium (n=4213)
Unadjusted Mean Annual Medical Costs ($US)	All-Cause	8889	8848	11,009	11,128
	COPD-Related	1148	1546	1691	1759
Adjusted Mean Annual Difference Medical Costs ($US)	All-Cause	-1735*	-1547*	255	REF
	COPD-Related	-326*	-227*	-67	REF
Unadjusted Mean Annual Prescription Costs ($US)	All-Cause	4355	4410	3963	4073
	COPD-Related	637	477	415	309
Adjusted Mean Annual Difference Pharmacy Costs ($US)	All-Cause	415*	247*	-80*	REF
	COPD-Related	333*	109*	42*	REF
Unadjusted Mean Annual Total Costs ($US)	All-Cause	13,244	13,258	14,972	15,201
	COPD-Related	1785	2023	2106	2067
Adjusted Mean Annual Difference Total Costs ($US)	All-Cause	NR	NR	NR	NR
	COPD-Related	NR	NR	NR	NR

*$P<0.05$ vs. ipratropium; NR=Not Reported; REF=Reference

Costs were standardized to 2004 $US

10.5 Compliance/Adherence with *Advair Diskus* in COPD

Studies Assessing Compliance with Advair Diskus in COPD

Study 1: Managed Care Plans Database

A retrospective, observational cohort study was conducted using medical and pharmacy claims data from a large managed care database encompassing more than 30 different managed care plans and 33 million patients across the U.S.[55,58] The study included 12,381 patients ≥40 years of age with a diagnosis of COPD (ICD-9 490.xx, 491.xx, 492.xx, or 496.xx) less than one year prior to initial treatment in an inhaled COPD medication. The initial COPD prescription (index date) was between January 2, 2001 and August 12, 2003. The patients were required to have 24 months of continuous eligibility – 12 months prior to and 12 months following the index date. The COPD medications included in the study were *Advair Diskus* 250/50 (n=1832), salmeterol alone (n=1099), ICS alone (n=3940), ipratropium plus albuterol in a single inhaler (n=3388), and ipratropium alone (n=2122).

Refill rates and medication possession ratio (MPR) were compared in the 12-month post-index period. Refill rate was defined as the number of prescriptions for a COPD medication dispensed during the 12-months following the index date. The MPR was calculated as the ratio of the sum of the number of therapy days supplied on all COPD medications dispensed during the 12 months following the index date divided by 365.

The refill rate for *Advair Diskus* 250/50 was higher (3.21) than salmeterol alone (2.31), ICS alone (1.94), ipratropium plus albuterol (2.56), or ipratropium alone (2.57). The MPR was also higher for *Advair Diskus* 250/50 (0.26) than salmeterol alone (0.19), ICS alone (0.16), ipratropium plus albuterol (0.21), or ipratropium alone (0.21).

In this study, initial maintenance therapy with *Advair Diskus* 250/50 was associated with a significant 32% lower risk of all-cause hospitalization or ED visit compared with ipratropium alone (adjusted HR = 0.685; 95% CI = 0.620, 0.757) and a significant 56% lower risk of COPD-related hospitalization or ED visit (adjusted HR = 0.442; 95% CI = 0.341, 0.573). Therapy with *Advair Diskus* was related to lower medical costs, higher pharmacy costs, and similar total costs.

Study 2: Healthcare Benefit Plans Database

A retrospective, cohort study was conducted using medical and pharmacy claims data from a database comprised of information from private healthcare benefit plans covering over 40 million patients enrolled in over 70 health plans across the U.S.[56] The study included 9466 patients 40-65 years of age with a diagnosis of COPD (ICD-9 491.xx, 492.xx, or 496.xx) but not asthma (493.xx). The initial COPD prescription (index date) was between July 1, 1998 and January 31, 2004. The patients were required to have 24 months of continuous eligibility – 12 months prior to and 12 months following the index date. The COPD medications included in the study were *Advair Diskus* 250/50 (n=921), salmeterol alone (n=859), ICS alone (n=2398), ipratropium plus albuterol (n=3863), and ipratropium alone (n=1425).

Refill rates and medication possession ratio (MPR) were compared in the 12-month post-index period. Refill rate was defined as the number of prescriptions for a COPD medication dispensed during the 12-months following the index date. The MPR was calculated as the ratio of the sum of the number of therapy days supplied on all COPD medications dispensed during the 12 months following the index date divided by 365.

The refill rate for *Advair Diskus* 250/50 (3.1) was significantly ($P \leq 0.03$) higher than salmeterol alone (2.8), ICS alone (2.2), ipratropium plus albuterol (2.8), or ipratropium alone (2.8). The MPR was also significantly ($P < 0.001$) higher for *Advair Diskus* 250/50 (0.27) than salmeterol alone (0.23), ICS alone (0.15), ipratropium plus albuterol (0.18), or ipratropium alone (0.17).

In this study, patients receiving initial maintenance therapy with *Advair Diskus* 250/50 had a significantly lower rate of all-cause hospitalizations or ED visits than those receiving initial therapy with ipratropium alone (37.0% vs. 43.3%; $P=0.003$). Patients receiving initial maintenance therapy with *Advair Diskus* 250/50 also had a significantly lower rate of COPD-related hospitalizations or ED visits (9.4% vs. 13.5%; $P=0.003$).

10.6 Studies Assessing Appropriate Use of *Advair Diskus*

Studies Assessing Appropriate Use of Advair Diskus

Drug Use Review activities are often conducted using pharmacy claims data to assess appropriate use of pharmaceutical products. When only pharmacy claims data are used, the assessment is limited because the diagnosis may not be known. These analyses may also be limited by the time frame selected, such as a 180-day time frame for assessing medications used in the treatment of asthma. Since patients taper their medications up and down according to their asthma control and this may vary over the period of a year, a 180-day time frame may be insufficient. Further, patients' eligibility for benefits may change over time, such as employees selecting insurance plans during open enrollment periods or patients cycling in and out of coverage in government sponsored programs such as Medicaid. Therefore, requiring longer eligibility times will also strengthen these analyses.

Study Design

Retrospective, observational, cohort analyses of administrative claims databases were conducted to assess the proportion of patients with documentation in their claims history that could identify them as appropriate candidates for use of *Advair Diskus*.[59,60] These analyses were conducted using patient-level data from pharmacy claims that were linked with medical claims and eligibility information.

In these analyses, two databases were utilized. A commercial database was used that included over 60 million managed care lives from over 45 health plans. It was nationally representative of U.S. lives of

patients <65 years of age with commercial health benefits. The MarketScan® Multi-State Medicaid Database included data from 7.4 million Medicaid lives from 8 states that varied in size and were geographically dispersed; there was at least one state from each U.S. census region.

Study subjects consisted of all patients in the databases who were 4 years and older who filled an *Advair Diskus* 100/50 or 250/50 prescription between January 1, 2006 and June 30, 2006. The first fill date within this period was identified as the "index date." Patients were required to have continuous eligibility in the plan for 36 months prior to the index date. A sensitivity analysis using 12 and 24 months eligibility time periods was also conducted.

Each patient was assessed for the following criteria. These criteria were used to determine appropriate patients for use of *Advair Diskus*.

- Primary criteria
  - prior fill of inhaled corticosteroid-containing medication
  - prior treatment by a specialist (pulmonologist or allergist)
  - prior asthma-related ED visit or hospitalization (primary diagnosis)
  - prior COPD diagnosis
  - anticholinergic prescription fill in patients ≥45 years of age
- Secondary criteria (in the 36-month period)
  - ≥7 fills for oral corticosteroid
  - ≥5 visits with primary asthma diagnosis
  - ≥2 spirometry tests
  - ≥7 fills for short-acting beta-agonist
  - ≥5 visits for asthma diagnosis (any diagnosis)
  - prior fill for leukotriene receptor antagonist

Managed Care Database

In the commercial database, 38,142 patient were identified filling *Advair Diskus* with a 36-month eligibility period.[59] Patients identified with the above criteria are summarized in Table 103. This assessment indicates that 87% (90% using primary and secondary criteria) of patients prescribed *Advair Diskus* had prior evidence in their claims history that could identify them as appropriate candidates for *Advair Diskus*.

Table 103. Proportion of Patients With Evidence of Appropriate Prescribing of *Advair Diskus* – Managed Care Databases[59]

	36 months		Sensitivity Analysis 24 months		Sensitivity Analysis 12 months	
Patients filling *Advair*	38,142	% of Patient Removed*	109,707	% of Patients Removed*	147,932	% of Patients Removed*
Prior COPD diagnosis or anticholinergic fill + ≥45 years	10,736	28%	85,591	22%	122,726	17%
Prior asthma-related ED visit or hospitalization	2,059	6%	79,902	5%	117,956	3%
Prior treatment by specialist	8,433	22%	56,392	21%	89,929	19%
Prior fill ICS-containing medication	12,101	31%	16,752	36%	31,104	40%
Total Primary Criteria	87%		85%		79%	
Any secondary criteria	885	3%	14,124	2%	26,940	3%
Total Primary Plus Secondary Criteria	90%		87%		82%	
*Patients identified meeting each defined criteria were removed from the cohort in the order specified.						

Medicaid Database

In the Medicaid database, 27,259 patient were identified filling *Advair Diskus* with a 36-month eligibility period.[60] Patients identified with the above criteria are summarized in Table 104. This assessment indicates that 92% (94% using primary and secondary criteria) of patients prescribed *Advair Diskus* had prior evidence in their claims history that could identify them as appropriate candidates for *Advair Diskus*.

Table 104. Proportion of Patients With Evidence of Appropriate Prescribing of *Advair Diskus* – Medicaid Databases[60]

	36 months		Sensitivity Analysis 24 months		Sensitivity Analysis 12 months	
Patients filling *Advair*	27,259	% of Patients Removed*	32,515	% of Patient Removed*	39,300	% of Patient Removed*
Prior COPD diagnosis or anticholinergic fill + ≥45 years	9,539	35%	10,281	32%	10,484	27%
Prior asthma-related ED visit or hospitalization	3,996	15%	3,849	12%	3,208	8%
Prior treatment by specialist	1,855	7%	2,162	7%	2,366	6%
Prior fill ICS-containing medication	9,517	35%	12,676	39%	16,607	42%
Total Primary Criteria	92%		90%		83%	
Any secondary criteria	492	2%	647	2%	945	2%
Total Primary Plus Secondary Criteria	94%		92%		85%	
*Patients identified meeting each defined criteria were removed from the cohort in the order specified.						

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Appendix

Table 80. Clinical Summary Table of *Advair Diskus* Compared with the Individual Components Alone in Adults and Adolescents with Asthma

Ref	Design & Duration	# Pts (Age)	Dose/Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Kavuru [7]	MC, R, DB, PG, PC 12 weeks	356 (≥12 yrs)	ADV (*Diskus*) 100/50 BID; FP (*Diskus*)100 mcg BID Sal (*Diskus*) 50 mcg BID PBO (*Diskus*) BID	• Diagnosis of asthma (ATS definition) • FEV_1 40-85% of predicted • Prior to the study, patients were either taking ICS alone or sal 50 mcg alone • ICS doses allowed prior to run-in were: BDP (252-420 mcg/day), TAA (600-1000 mcg/day), flunisolide (1000 mcg/day), FP (176 mcg/day)	**Primary Endpoints:** % of patients that withdrew due to lack of efficacy: ADV: 3% FP: 11% Sal: 35% PBO: 49% ($P \leq 0.020$ ADV vs PBO, Sal, FP) Mean change from baseline in morning pre-dose FEV_1: ADV: 0.51 L (25%) FP: 0.28 L (15%) Sal: 0.11 L (5%) PBO: 0.01 L (1%) ($P \leq 0.027$, ADV vs PBO, Sal, FP)	• All treatment groups were well-tolerated • Most common drug-related adverse events included hoarseness, dysphonia, candidiasis, headache, and tremor • No significant differences in mean heart rate or occurrence ventricular or supraventricular ectopy • No significant ECG changes

MC=multicenter; R=randomized; DB=double blind; PG=parallel group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=salmeterol; PBO=placebo; FEV_1=forced expiratory volume in one second; ATS=American Thoracic Society; ICS=inhaled corticosteroid; BDP=beclomethasone dipropionate; TAA=triamcinolone acetonide; AUC=area under the curve; AM=morning; PM=evening; PEF=peak expiratory flow; ECG=electrocardiograph; AE=adverse event; DD=double-dummy; BUD=budesonide

Ref	Design & Duration	# Pts (Age)	Dose/Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Kavuru (cont.)					Mean 12-hr Serial FEV_1 AUC Relative to baseline at Week 1, L-hours ADV: 7.67; FP: 3.58; Sal: 4.90; PBO: 2.56 ($P \leq 0.027$, ADV vs PBO, Sal, FP) **Secondary Endpoints:** • Significant improvements in AM and PM PEF with ADV vs. other comparative arms **Other Efficacy Endpoints**: • Significant improvements in symptom scores and reduction in albuterol use with ADV vs. other comparative arms • Significant improvements in nights with no awakenings with ADV vs. PBO & Sal	

MC=multicenter; R=randomized; DB=double blind; PG=parallel group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=salmeterol; PBO=placebo; FEV_1=forced expiratory volume in one second; ATS=American Thoracic Society; ICS=inhaled corticosteroid; BDP=beclomethasone dipropionate; TAA=triamcinolone acetonide; AUC=area under the curve; AM=morning; PM=evening; PEF=peak expiratory flow; ECG=electrocardiograph; AE=adverse event; DD=double-dummy; BUD=budesonide

Ref	Design & Duration	# Pts (Age)	Dose/Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Shapiro[215]	MC, R, DB, PG, PC 12 weeks	349 (≥12 yrs)	ADV (*Diskus*) 250/50 BID; FP (*Diskus*) 250 mcg BID Sal (*Diskus*) 50 mcg BID PBO (*Diskus*) BID	• Diagnosis of asthma (ATS definition) • FEV_1 40-85% of predicted • Prior to the study, patients were either taking medium to high dose of ICS for ≥4 weeks (BDP (462-672 mcg/day), TAA (1100-1600 mcg/day), flunisolide (1250-2000 mcg/day), FP (440 mcg/day)	**Primary Endpoints:** % of patients that withdrew due to lack of efficacy: ADV: 4% FP: 22% Sal: 38% PBO: 62% (P≤0.002 ADV vs PBO, Sal, FP) Mean change from baseline in morning pre-dose FEV_1: ADV: 0.48 L (23%) FP: 0.25 L (13%) Sal: 0.05 L (4%) PBO: -0.11 L (-5%) (P≤0.028 vs PBO, Sal, FP) Mean 12-hr Serial FEV_1 AUC Relative to baseline at Week 1 (L-hours) ADV: 6.71 FP: 2.01 Sal: 3.78	• All treatments well tolerated • Most AEs (≥2%) were candidiasis and cough • No significant changes in 12-lead ECG. • No clinically significant differences were noted in plasma cortisols or cosyntropin stimulation testing

MC=multicenter; R=randomized; DB=double blind; PG=parallel group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=salmeterol; PBO=placebo; FEV_1=forced expiratory volume in one second; ATS=American Thoracic Society; ICS=inhaled corticosteroid; BDP=beclomethasone dipropionate; TAA=triamcinolone acetonide; AUC=area under the curve; AM=morning; PM=evening; PEF=peak expiratory flow; ECG=electrocardiograph; AE=adverse event; DD=double-dummy; BUD=budesonide

Ref	Design & Duration	# Pts (Age)	Dose/Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Shapiro (cont)					PBO: -0.09 *P*<0.03 ADV vs PBO, Sal, FP) **Secondary Endpoints:** • Significant improvements in AM and PM PEF with ADV vs. other comparative arms **Other Efficacy Endpoints:** • Significant improvements in symptom scores, nights with no awakenings and reduction in albuterol use with ADV vs. other comparative arms	

MC=multicenter; R=randomized; DB=double blind; PG=parallel group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=salmeterol; PBO=placebo; FEV_1=forced expiratory volume in one second; ATS=American Thoracic Society; ICS=inhaled corticosteroid; BDP=beclomethasone dipropionate; TAA=triamcinolone acetonide; AUC=area under the curve; AM=morning; PM=evening; PEF=peak expiratory flow; ECG=electrocardiograph; AE=adverse event; DD=double-dummy; BUD=budesonide

Ref	Design & Duration	# Pts (Age)	Dose/Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Aubier [9,216]	MC, R, DB, DD, PG 28 weeks (first 12 weeks efficacy measures collected; entire 28 weeks safety measures collected)	503 (≥12 yrs)	ADV (*Diskus*) 500/50 BID FP (*Diskus*) 500 mcg BID + salmeterol (*Diskus*) 50 mcg BID FP (*Diskus*) 500 mcg BID	• Clinical history of reversible airway disease • Receiving an ICS for ≥12 weeks • Received the following ICS doses for ≥4 weeks (BDP 1500-2000 mcg/day, BUD 1500-2000 mcg day, FP 750-1000 mcg/day) • Symptomatic during 2-wk run-in on their current dose of ICS	**Primary Endpoints:** Mean change from baseline in AM PEF over weeks 1-12: ADV: 35 L/min FP + Sal: 33 L/min FP: 15 L/min Mean treatment difference ADV vs FP + Sal = -3 L/min (90% CI –10,4; *P*=0.535) Mean treatment difference ADV vs FP=-21 L/min (90% CI -29, -12; *P*<0.001) **Secondary Endpoints:** • Significant improvement with ADV vs. FP in PM PEF, % of symptom-free days, % of albuterol-free days	• All treatment groups were well tolerated • Most common adverse events (≥2%) included asthma, breathing disorders, cough, hoarseness/ dysphonia, throat irritation, and headache • No significant differences between groups in change in serum cortisol levels or 24-hour urinary cortisol after 28 weeks

MC=multicenter; R=randomized; DB=double blind; PG=parallel group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=salmeterol; PBO=placebo; FEV_1=forced expiratory volume in one second; ATS=American Thoracic Society; ICS=inhaled corticosteroid; BDP=beclomethasone dipropionate; TAA=triamcinolone acetonide; AUC=area under the curve; AM=morning; PM=evening; PEF=peak expiratory flow; ECG=electrocardiograph; AE=adverse event; DD=double-dummy; BUD=budesonide

Ref	Design & Duration	# Pts (Age)	Dose/Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Aubier (cont.)					• Improvement with ADV vs. FP was seen in % of symptom-free nights and FEV_1, but these difference were not statistically significant • Comparable improvements were seen between ADV and FP + Sal in these secondary endpoints	

MC=multicenter; R=randomized; DB=double blind; PG=parallel group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=salmeterol; PBO=placebo; FEV_1=forced expiratory volume in one second; ATS=American Thoracic Society; ICS=inhaled corticosteroid; BDP=beclomethasone dipropionate; TAA=triamcinolone acetonide; AUC=area under the curve; AM=morning; PM=evening; PEF=peak expiratory flow; ECG=electrocardiograph; AE=adverse event; DD=double-dummy; BUD=budesonide

Table 81. Clinical Summary Table of *Advair Diskus* In Children 4-11 Years with Asthma

Ref	Design & Duration	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy Endpoints	Safety Results
Van den Berg[15,217]	MC, R, DB, DD, PG 12 weeks	257 (4-11 years)	ADV (*Diskus*) 100/50 BID FP (*Diskus*) 100 mcg BID + Sal (*Diskus*) 50 mcg BID	• Children with reversible airway obstruction • Remained symptomatic on ICS alone (BDP, BUD or flunisolide at a dose of 400-500 mcg/day or FP 200-250 mcg/day)	**Primary Endpoint:** AM PEF, Mean Change from Baseline Over Weeks 1-12 ADV: 33 L/min; FP + Sal: 28 L/min Mean treatment difference = -5 L/min (90% CI –10, 0; *P*=0.103) **Secondary Endpoint:** • No significant differences between treatments in change in PM PEF, % symptom-free days, % symptom-free nights, % albuterol-free days, albuterol-free nights, and FEV_1	• Both treatment groups were well tolerated • Most common drug-related adverse events included candidiasis mouth/throat (2% and 2%), malaise and fatigue (<1% and 2%), candidiasis (unspecified site) (2% and 0%), aggression and hostility (<1% and 2%), and lower respiratory tract disorder (<1% and 2%) • No significant differences were observed between groups for morning plasma cortisol concentrations

MC=multicenter; R=randomized; DB=double-blind; DD=double-dummy; PG=parallel-group; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=salmeterol; ICS=inhaled corticosteroid; BDP=beclomethasone dipropionate; BUD=budesonide; AM=morning; PEF=peak expiratory flow; FEV_1=forced expiratory volume in one second; TAA=triamcinolone acetonide; SABA=short-acting $beta_2$-agonist

Ref	Design & Duration	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy Endpoints	Safety Results
Malone [16]	MC, R, DB, PG 12 weeks	203 (4-11 years)	ADV (*Diskus*) 100/50 BID FP (*Diskus*) 100 mcg BID	• Diagnosis of asthma for ≥2 months • Receiving an ICS (BDP 252-336 mcg/day, TAA 600-1,000 mcg/day, flunisolide 1,000 mcg/day, FP 88-250 mcg/day, or BUD 200-400 mcg/day) at a consistent dose for ≥1 month • AM PEF (ages 4-5) or FEV_1 (ages 6-11) 50%-95% of predicted at baseline • Symptomatic on current ICS	The primary objective of this study was safety; secondary efficacy measures were collected, but no power calculations were performed	• Incidence of AEs reported were generally similar between treatment groups • The values for 24-hour urinary cortisol excretion at baseline and after 12 weeks of treatment were similar within and between treatment groups • Hematology and chemistry values were in the normal range for all but 3 patients in each group • For all patients in both groups at 12 weeks, ECGs, mean heart rate, QTc intervals, and vital signs were considered normal or comparable to baseline values, as well as similar between groups. • Incidence of asthma exacerbations (3% and 8%) and withdrawals due to an asthma exacerbation (2% and 5%) were lower with ADV compared with FP

MC=multicenter; R=randomized; DB=double-blind; DD=double-dummy; PG=parallel-group; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=salmeterol; ICS=inhaled corticosteroid; BDP=beclomethasone dipropionate; BUD=budesonide; AM=morning; PEF=peak expiratory flow; FEV_1=forced expiratory volume in one second; TAA=triamcinolone acetonide; SABA=short-acting $beta_2$-agonist

Table 82. Clinical Summary Table of *Advair HFA* Compared with the Individual Components Alone in Adults and Adolescents with Asthma

Ref	Design & Duration	# Pts (Age)	Dose/Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Pearl-man[62]	MC, R, DB, PG, PC 12 weeks	360 (≥12 yrs)	ADV (HFA MDI) 45/21, 2 puffs BID; FP (CFC MDI) 44 mcg, 2 puffs BID Sal (CFC MDI) 21 mcg, 2 puffs BID PBO (HFA MDI) BID	• ≥12 years • Diagnosis of asthma (ATS definition) • FEV_1 40-85% of predicted • Prior to the study, patients were either taking ICS, LABA, or SABA alone	**Primary Endpoints: *Advair HFA* vs. Salmeterol** % of patients that withdrew due to lack of efficacy: ADV: 2% FP: 8% Sal: 25% PBO: 28% (*P*<0.001 ADV vs PBO & Sal) Mean change from baseline in morning pre-dose FEV_1 at Endpoint: ADV: 0.58 L (27%), FP: 0.36 L (18%) Sal: 0.25 L (12%) PBO: 0.14 L (5%) (*P*<0.004, ADV vs PBO, Sal, FP)	• All treatment groups were well-tolerated • Most commonly occurring (≥2%) drug-related adverse events were throat irritation, hoarseness/dysphonia, headache, and cough • No clinically significant unfavorable changes in ECG or 24-hour ambulatory electrocardiography after 12 weeks of treatment with any treatment • No clinically relevant differences between groups in laboratory assessments

MC=multicenter; R=randomized; DB=double blind; PG=parallel group; PC=placebo-controlled; Yrs=Years; ADV=*Advair*; HFA=hydrofluroalkane; MDI=metered-dose inhaler; BID=twice daily; FP=fluticasone propionate; CFC=chloroflurocarbon; Sal=salmeterol; PBO=placebo; ATS=American Thoracic Society; FEV_1=forced expiratory volume in one second; ICS=inhaled corticosteroid; LABA=long-acting $beta_2$-agonist; SABA=short-acting $beta_2$-agonist; BDP=beclomethasone dipropionate; BUD=budesonide; TAA=triamcinolone acetonide; AM=morning; PM=evening; PEF=peak expiratory flow; AUC=area under the curve; ECG=electrocardiograph; DD=double dummy

Ref	Design & Duration	# Pts (Age)	Dose/Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Pearlman (cont.)				• ICS doses allowed prior to run-in were: BDP (252-336 mcg/day), TAA (600-800 mcg/day), flunisolide (1000 mcg/day), FP (176 mcg/day via MDI or 200 mcg/day inhalation powder), BUD (400-600 mcg/day)	**Primary Endpoint: *Advair HFA* vs. FP** Mean 12-hr Serial FEV_1 AUC Relative to baseline at Day 1, (L-hr) ADV: 6.7; FP: 2.7; Sal: 6.1; PBO: 2.0 ($P<0.001$, ADV vs PBO & FP) Mean 12-hr Serial FEV_1 AUC Relative to baseline at Week 12,(L-hr) ADV: 9.0; FP: 5.6; Sal: 6.5; PBO: 2.6 ($P\leq0.006$, ADV vs PBO, FP & Sal) **Secondary Endpoints:** • Significant improvements in AM and PM PEF with ADV vs. other comparative arms • Significant improvements in symptom scores and reduction in albuterol use with ADV vs. other comparative arms • Significant improvements in nights with no awakenings with ADV vs. other comparative arms	

MC=multicenter; R=randomized; DB=double blind; PG=parallel group; PC=placebo-controlled; Yrs=Years; ADV=*Advair*; HFA=hydrofluroalkane; MDI=metered-dose inhaler; BID=twice daily; FP=fluticasone propionate; CFC=chloroflurocarbon; Sal=salmeterol; PBO=placebo; ATS=American Thoracic Society; FEV_1=forced expiratory volume in one second; ICS=inhaled corticosteroid; LABA=long-acting $beta_2$-agonist; SABA=short-acting $beta_2$-agonist; BDP=beclomethasone dipropionate; BUD=budesonide; TAA=triamcinolone acetonide; AM=morning; PM=evening; PEF=peak expiratory flow; AUC=area under the curve; ECG=electrocardiograph; DD=double dummy

Ref	Design & Duration	# Pts (Age)	Dose/Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Nelson [64]	MC, R, DB, PG 12 weeks	283 (≥12 yrs)	ADV (HFA MDI) 45/21, 2 puffs BID; FP (CFC MDI) 44 mcg, 2 puffs BID Sal (CFC MDI) 21 mcg, 2 puffs BID	• Diagnosis of asthma (ATS definition) • FEV_1 40-85% of predicted • Symptomatic on as-needed SABA alone	**Primary Endpoints: *Advair HFA* vs. Salmeterol** Mean change from baseline in morning pre-dose FEV_1 at Endpoint: ADV: 0.69 L (33%) FP: 0.51 L (25%) Sal: 0.47 L (22%) $P \leq 0.016$ ADV vs Sal & FP **Primary Endpoint: *Advair HFA* vs. FP** Mean 12-hr Serial FEV_1 AUC Relative to baseline at Day 1 (L-hours) ADV: 7.2; FP: 2.9; Sal: 7.6 $P \leq 0.016$ ADV vs FP Mean 12-hr Serial FEV_1 AUC Relative to baseline at Week 12,(L-hr) ADV: 10.6; FP: 7.2; Sal: 8.2 ($P \leq 0.016$, ADV vs FP & Sal)	• *Advair HFA* had a similar safety profile to the individual agents • Most commonly occurring (≥2%) drug-related adverse events were throat irritation, hoarseness/dysphonia, headache, candidiasis of mouth or throat, and cough

MC=multicenter; R=randomized; DB=double blind; PG=parallel group; PC=placebo-controlled; Yrs=Years; ADV=*Advair*; HFA=hydrofluroalkane; MDI=metered-dose inhaler; BID=twice daily; FP=fluticasone propionate; CFC=chloroflurocarbon; Sal=salmeterol; PBO=placebo; ATS=American Thoracic Society; FEV_1=forced expiratory volume in one second; ICS=inhaled corticosteroid; LABA=long-acting beta$_2$-agonist; SABA=short-acting beta$_2$-agonist; BDP=beclomethasone dipropionate; BUD=budesonide; TAA=triamcinolone acetonide; AM=morning; PM=evening; PEF=peak expiratory flow; AUC=area under the curve; ECG=electrocardiograph; DD=double dummy

Ref	Design & Duration	# Pts (Age)	Dose/Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Nelson (cont)					**Secondary Endpoints:** • Significant improvements in AM and PM PEF with ADV vs. other comparative arms • Improvements in symptom scores, nights with no awakenings and reduction in albuterol use were seen across treatment groups with no statistically significant difference between treatments	

MC=multicenter; R=randomized; DB=double blind; PG=parallel group; PC=placebo-controlled; Yrs=Years; ADV=*Advair*; HFA=hydrofluroalkane; MDI=metered-dose inhaler; BID=twice daily; FP=fluticasone propionate; CFC=chloroflurocarbon; Sal=salmeterol; PBO=placebo; ATS=American Thoracic Society; FEV_1=forced expiratory volume in one second; ICS=inhaled corticosteroid; LABA=long-acting $beta_2$-agonist; SABA=short-acting $beta_2$-agonist; BDP=beclomethasone dipropionate; BUD=budesonide; TAA=triamcinolone acetonide; AM=morning; PM=evening; PEF=peak expiratory flow; AUC=area under the curve; ECG=electrocardiograph; DD=double dummy

Ref	Design & Duration	# Pts (Age)	Dose/Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Nathan[127]	MC, R, DB, PG, PC 12 weeks	365 (≥12 yrs)	ADV (HFA MDI) 115/21, 2 puffs BID; FP (CFC MDI) 110 mcg, 2 puffs BID Sal (CFC MDI) 21 mcg, 2 puffs BID PBO (HFA MDI) BID	• Diagnosis of asthma (ATS definition) • FEV_1 40-85% of predicted • Prior ICS use for ≥ 3 months	**Primary Endpoints: *Advair HFA* vs. Salmeterol** Mean change from baseline in morning pre-dose FEV_1 at Endpoint: ADV: 0.41 L (20%) FP: 0.19 L (9%) Sal: 0.15 L (8%) PBO: -0.12 L (-6%) *P*≤0.001 ADV vs FP, Sal, PBO % of patients that withdrew due to lack of efficacy: ADV: 7% FP: 11% Sal: 24% PBO: 54% (*P*≤0.001 ADV vs PBO & Sal) **Primary Endpoint: *Advair HFA* vs. FP** Mean 12-hr Serial FEV_1 AUC Relative to baseline at Day 1,(L-hr) ADV: 5.4; FP: 2.1; Sal: 6.1; PBO: 0.6 (*P*<0.001, ADV vs PBO & FP)	• *Advair HFA* had a similar safety profile to the individual agents • Most commonly occurring (≥2%) drug-related adverse events were throat irritation, headache, candidiasis of mouth/throat, unspecified oropharyngeal plaques, palpitations • No clinically significant changes from baseline in ECG changes, blood pressure, or heart rate • No differences between treatment groups in plasma or urinary cortisol concentrations

MC=multicenter; R=randomized; DB=double blind; PG=parallel group; PC=placebo-controlled; Yrs=Years; ADV=*Advair*; HFA=hydrofluroalkane; MDI=metered-dose inhaler; BID=twice daily; FP=fluticasone propionate; CFC=chloroflurocarbon; Sal=salmeterol; PBO=placebo; ATS=American Thoracic Society; FEV_1=forced expiratory volume in one second; ICS=inhaled corticosteroid; LABA=long-acting $beta_2$-agonist; SABA=short-acting $beta_2$-agonist; BDP=beclomethasone dipropionate; BUD=budesonide; TAA=triamcinolone acetonide; AM=morning; PM=evening; PEF=peak expiratory flow; AUC=area under the curve; ECG=electrocardiograph; DD=double dummy

Ref	Design & Duration	# Pts (Age)	Dose/Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Nathan (cont.)				• ICS doses allowed prior to run-in were: BDP (378-840 mcg/day), TAA (900-1600 mcg/day), flunisolide (1250-2000 mcg/day), FP (440-660 mcg/day via MDI or 400-600 mcg/day inhalation powder), BUD (800-1200 mcg/day)	Mean 12-hr Serial FEV_1 AUC Relative to baseline at Week 12,(L-hr) ADV: 7.0; FP: 3.6; Sal: 5.3; PBO: 1.4 ($P \leq 0.02$, ADV vs PBO, FP & Sal) **Secondary Endpoints:** • Significant improvements in AM PEF, PM PEF, and reduction in albuterol use with ADV vs. other comparative arms • Improvements in symptom scores and nights with no awakenings were significantly improved vs. PBO	

MC=multicenter; R=randomized; DB=double blind; PG=parallel group; PC=placebo-controlled; Yrs=Years; ADV=*Advair*; HFA=hydrofluroalkane; MDI=metered-dose inhaler; BID=twice daily; FP=fluticasone propionate; CFC=chloroflurocarbon; Sal=salmeterol; PBO=placebo; ATS=American Thoracic Society; FEV_1=forced expiratory volume in one second; ICS=inhaled corticosteroid; LABA=long-acting $beta_2$-agonist; SABA=short-acting $beta_2$-agonist; BDP=beclomethasone dipropionate; BUD=budesonide; TAA=triamcinolone acetonide; AM=morning; PM=evening; PEF=peak expiratory flow; AUC=area under the curve; ECG=electrocardiograph; DD=double dummy

Ref	Design & Duration	# Pts (Age)	Dose/Schedule	Inclusion Criteria	Efficacy Results	Safety Results
van Noord[128]	MC, R, DB, DD, PG 12 weeks Designed to demonstrate superiority of ADV HFA over FP and equivalence between ADV HFA and ADV *Diskus* No comparisons were made between ADV *Diskus* and FP	509 (≥12 yrs)	ADV (HFA MDI) 230/21, 2 puffs BID; FP (CFC MDI) 220 mcg, 2 puffs BID ADV (*Diskus*) 500/50, 1 inhalation BID	• Diagnosis of asthma (ATS definition) • FEV_1 > 50% of predicted • AM PEF 50-85% after albuterol • Symptomatic on ICS (BDP, BUD or flunisolide 1500-2000 mcg/day or FP 750-100 mcg/day) for at least 4 weeks	**Primary Endpoint: Adjusted Mean Change in Morning Pre-Dose PEF Over Weeks 1-12:** ADV HFA: 50 L/min ADV *Diskus*: 48 L/min FP: 27 L/min P<0.001 *Advair HFA* vs. FP **Secondary Endpoints:** • Significant improvement in PM PEF, AM and PM asthma symptoms, albuterol use, and clinic FEV_1 for ADV HFA vs. FP • Comparable results were seen between ADV HFA and ADV *Diskus* for these secondary endpoints	• All treatments were well tolerated • Drug-related AEs were reported in 13%, 11%, and 13% of patients in the ADV HFA, ADV *Diskus*, and FP, respectively • Serum cortisol levels were lower at Week 12 with ADV *Diskus* vs. HFA (*P* = 0.014) but not between ADV HFA and FP • No significant differences in urinary cortisol excretion between the groups • No clinically significant differences between groups heart rate, QTc interval or other laboratory assessments

MC=multicenter; R=randomized; DB=double blind; PG=parallel group; PC=placebo-controlled; Yrs=Years; ADV=*Advair*; HFA=hydrofluroalkane; MDI=metered-dose inhaler; BID=twice daily; FP=fluticasone propionate; CFC=chloroflurocarbon; Sal=salmeterol; PBO=placebo; ATS=American Thoracic Society; FEV_1=forced expiratory volume in one second; ICS=inhaled corticosteroid; LABA=long-acting $beta_2$-agonist; SABA=short-acting $beta_2$-agonist; BDP=beclomethasone dipropionate; BUD=budesonide; TAA=triamcinolone acetonide; AM=morning; PM=evening; PEF=peak expiratory flow; AUC=area under the curve; ECG=electrocardiograph; DD=double dummy

Table 83. Clinical Summary of *Advair* Compared with Budesonide Formoterol Combination for the Treatment of Asthma

Ref	Design & Duration	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Busse[22,218,219]	MC, R, OL, PG 7 months	1225 (≥12 yrs)	**Treatment Phase I (1 month):** ADV (*Diskus*) SD 250/50, 1 inhalation BID BFC (HFA MDI) SD 160/4.5, 2 inhalations BID **Treatment Phase II (6 months):** ADV (*Diskus*) SD 250/50, 1 inhalation BID BFC (HFA MDI) SD 160/4.5 2 inhalations BID BFC (HFA MDI) AMD 160/4.5 (2-4 inhalations BID)	• Diagnosis of asthma • $FEV_1 \geq 50$ % predicted • Previously treated with ICS ± LABA • Randomized to treatment if symptomatic during a 2-week run-in	**Primary Endpoint:** Exacerbations, Number (% of Patients): ADV SD: 37 (9.2%) BFC SD: 37 (8.8%) BFC AMD: 31 (8.0%) *P*=NS between all treatments comparisons Exacerbations, Per Patient Per Treatment Year ADV SD: 0.189 BFC SD: 0.24 BFC AMD: 0.196; *P*=NS between all treatments comparisons	• The incidence of adverse events were similar among treatment groups • No significant differences or clinically relevant changes in pulse rate, systolic and diastolic blood pressures for any treatment group
Busse (cont)					**Secondary Endpoints:** Improvements in FEV_1, morning PEF, asthma symptoms, and rescue medication use were similar between treatment groups for the overall randomized treatment period	

MC=multicenter; R=randomized; OL=open-label; PG=parallel-group; ADV=Advair Diskus; SD=stable dose; BFC=budesonide formoterol combination; HFA=hydrofluroalkane; MDI=metered-dose inhaler; BID=twice daily; AMD=adjustable maintenance dosing; FEV_1=forced expiratory volume in one second; ICS=inhaled corticosteroid; LABA=long-acting $beta_2$-agonist; NS=non-significant; PEF=peak expiratory flow; DB=double-blind; DD=double-dummy; BDP=beclomethasone dipropionate

Ref	Design & Duration	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Dahl[23]	MC, R, DB, DD, PG 24 weeks	1391 (≥18 years)	ADV (*Diskus*) 250/50, 1 inhalation BID; BFC (Turbuhaler) 200/6, 2 inhalations BID	• Persistent asthma • FEV_1 ≥50% and reversibility ≥12% • ICS 1000-2000 mcg/day of BDP or equivalent • Randomized to treatment if symptomatic during a 2-week run-in	**Primary Endpoint:** Exacerbations, Adjusted mean rate: ADV: 2.69 BFC: 2.79 $P = 0.571$ **Secondary Endpoints:** Improvements in FEV_1, morning PEF, % symptom-free days and nights, % rescue-free days and nights were similar between treatment groups	• Both groups showed similar incidence and type of adverse events • Most commonly reported drug-related adverse events were hoarseness/ dysphonia (2% each), candidiasis of the mouth/throat (ADV 2%; BFC 1%), and headaches (ADV 1%; BFC 2%)
Kuna[190]	MC, R, DB, DD 6 months	2230 (≥12 yrs)	ADV HFA SD 125/25, 2 inhalations BID plus PRN terbutaline BFC (Turbuhaler) 160/4.5, 1 inhalation BID plus PRN doses BFC (Turbuhaler) SD 320/9 BID plus PRN terbutaline .	• Persistent asthma • FEV_1 ≥50% and reversibility ≥12% • ICS [≥500 mcg/day BUD or fluticasone (or ≥ 1000 mcg/day of another ICS)	**Primary Endpoint:** Time to first severe exacerbation: No significant difference SD Advair HFA vs SD BFC. **Secondary Endpoints:** Advair HFA SD had fewer # inhalations/day rescue medication vs SD BFC ($P \leq 0.05$).	• No notable differences in number or severity of adverse events. • Most commonly reported adverse events were upper respiratory tract infection, pharyngitis, and nasopharyngitis

MC=multicenter; R=randomized; OL=open-label; PG=parallel-group; ADV=Advair Diskus; SD=stable dose; BFC=budesonide formoterol combination; HFA=hydrofluroalkane; MDI=metered-dose inhaler; BID=twice daily; AMD=adjustable maintenance dosing; FEV_1=forced expiratory volume in one second; ICS=inhaled corticosteroid; LABA=long-acting $beta_2$-agonist; NS=non-significant; PEF=peak expiratory flow; DB=double-blind; DD=double-dummy; BDP=beclomethasone dipropionate

Ref	Design & Duration	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy Results	Safety Results
				• at least 1 asthma exacerbation in prior 12 months • Randomized to treatment if symptomatic during a 2-week run-in	No significant differences between SD treatments in other secondary endpoints including asthma symptoms, nighttime awakenings, asthma control days, rescue-free days, number of mild exacerbations, the number of severe exacerbations and other measures of lung function.	• Serious adverse events: 3% in SD Advair HFA and 4% in SD BFC. • 1 serious drug-related adverse event in Advair HFA group (asthma).
DOF[24]	MC, R DB, PG 12 weeks	248 adults	ADV (*Diskus*) 250/50, 1 inhalation BID BFC (Turbuhaler) 200/6, 1 inhalation BID	• moderate asthma • FEV_1 50% to 80% of predicted • ≥15% FEV_1 reversibility • ICS 1000 mcg/day of BDP or equivalent • symptomatic	**Primary Endpoint:** FEV_1 % predicted after 12 weeks ADV 78.8% vs BFC 76.5%; not significant (P=0.082). **Secondary Endpoints:** Mean proportion of days without symptoms increased from 10.4 to 37.3 for ADV and from 16.9 to 37.5 for BFC Mean proportion of days without rescue medication increased from 12.5 to 37.8 for ADV and from 16.6 to 40.4 for BFC.	• Treatment emergent adverse events: 36% for ADV and 31% for BFC.

MC=multicenter; R=randomized; OL=open-label; PG=parallel-group; ADV=Advair Diskus; SD=stable dose; BFC=budesonide formoterol combination; HFA=hydrofluroalkane; MDI=metered-dose inhaler; BID=twice daily; AMD=adjustable maintenance dosing; FEV_1=forced expiratory volume in one second; ICS=inhaled corticosteroid; LABA=long-acting $beta_2$-agonist; NS=non-significant; PEF=peak expiratory flow; DB=double-blind; DD=double-dummy; BDP=beclomethasone dipropionate

Table 84. Clinical Summary Table of *Advair Diskus* 250/50 versus Individual Components Alone in Patients with COPD

Ref	Design & Duration	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy	Safety
Hanania (45,120)	MC, R, DB, PG, PC 24 weeks	723 (mean age=63-65 years)	ADV (*Diskus*) 250/50 BID FP (*Diskus*) 250 mcg BID Sal (*Diskus*) 50 mcg BID PBO (*Diskus*) BID	• ≥40 years old • Current or former smoker (≥20 pack years) • COPD diagnosis • FEV_1/FVC ≤70% (and baseline FEV_1 <65% predicted but >0.7 L or if ≤0.7 L, then >40% of predicted normal) • Symptoms of chronic bronchitis • Moderate dyspnea	**Primary Endpoints:** Mean Morning Pre-dose FEV_1, change from baseline at Endpoint ADV: 165 ml (17%) FP: 109 ml (11%) Sal: 91 ml (9%) PBO: 1 ml (1%) *P*≤0.012 ADV vs Sal, PBO Mean 2-Hour Postdose FEV_1 (change from baseline at Endpoint): ADV: 281 ml (27%) FP: 147 ml (14%) Sal: 200 ml (19%) PBO: 58 ml (6%) *P*<0.001 ADV vs FP, PBO **Secondary/Other Efficacy Endpoints** (Mean Change from Baseline)	• Incidence of AEs was similar between groups except for an increase in oral candidiasis in the ADV and FP groups

*minimal clinically important change = 1.7 units; †minimal clinically important change = 10 units

MC=multicenter; R=randomized; DB=double-blind; PG=parallel-group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=salmeterol; PBO=placebo; COPD=chronic obstructive pulmonary disease; ATS=American Thoracic Society; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; AM=morning; PEF=peak expiratory flow; TDI=transition dyspnea index; CRDQ=chronic respiratory disease questionnaire; AE=adverse events; OCS=oral corticosteroid

Ref	Design & Duration	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy	Safety
Hanania (cont.)					AM PEF (L/min): ADV 30.6; FP 11.3; Sal 14.7; PBO 0.8 ($P < 0.05$ vs. FP, Sal, PBO) Dyspnea (TDI score)*: ADV 1.7; FP 1.7; Sal 1.6; PBO 1.0 ($P < 0.05$ vs. PBO) Albuterol Use (puffs/day): ADV -1.0; FP -0.2; Sal -0.7; PBO 0.1 ($P < 0.05$ vs. FP & PBO) Number of awakenings per night requiring albuterol use: ADV -0.12; FP -0.03; Sal -0.06; PBO 0.02 ($P < 0.05$ vs. PBO & Sal) Health status (CRDQ)†: ADV 10.0; FP 10.4; Sal 6.4; PBO 5.0 ($P < 0.05$ vs. PBO)	

*minimal clinically important change = 1.7 units; †minimal clinically important change = 10 units

MC=multicenter; R=randomized; DB=double-blind; PG=parallel-group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=salmeterol; PBO=placebo; COPD=chronic obstructive pulmonary disease; ATS=American Thoracic Society; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; AM=morning; PEF=peak expiratory flow; TDI=transition dyspnea index; CRDQ=chronic respiratory disease questionnaire; AE=adverse events; OCS=oral corticosteroid

Ref	Design & Duration	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy	Safety
Fergu-son[126,47]	MC, R, DB, PG 52 weeks	782 (mean age=65)	ADV (*Diskus*) 250/50 BID Sal (*Diskus*) 50 mcg BID	• ≥40 years old • Current or former smoker (≥10 pack years) • COPD diagnosis • Pre-bronchodilator FEV_1 ≤50% predicted • FEV_1/FVC ≤70% • ≥1 COPD exacerbation in prior 12 months	**Primary Endpoint:** Mean annual rate of moderate/severe exacerbations of COPD ADV: 1.06 Sal: 1.53 (Treatment ratio 0.695;*P* <0.001) **Secondary Endpoints:** Time to first moderate/severe exacerbation 25% Risk Reduction with ADV [HR 0.75 9*P* =0.003)] COPD exacerbations requiring OCS ADV 0.66 Sal 1.09 (Treatment ratio 0.603;*P* <0.001)	• The most common AEs across both groups were nasopharyngitis and pharyngolaryngeal pain which occurred in a similar percentage of patients in each group. • Pneumonia occurred more frequently in the ADV group (6% ADV and 2% Sal). • Dysphonia (4% ADV and <1% Sal), and candidiasis-related events(4% ADV and 2% Sal) occurred more frequently with ADV.

*minimal clinically important change = 1.7 units; †minimal clinically important change = 10 units

MC=multicenter; R=randomized; DB=double-blind; PG=parallel-group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=salmeterol; PBO=placebo; COPD=chronic obstructive pulmonary disease; ATS=American Thoracic Society; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; AM=morning; PEF=peak expiratory flow; TDI=transition dyspnea index; CRDQ=chronic respiratory disease questionnaire; AE=adverse events; OCS=oral corticosteroid

Ref	Design & Duration	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy	Safety
Data on file[46]	MC, R, DB, PG 52 weeks	797 (mean age=65)	ADV (*Diskus*) 250/50 BID Sal (*Diskus*) 50 mcg BID	• ≥40 years old • Current or former smoker (≥10 pack years) • COPD diagnosis • Pre-bronchodilator FEV_1 ≤50% predicted • FEV_1/FVC ≤70% • ≥1 COPD exacerbation in prior 12 months	**Primary Endpoints:** Mean annual rate of moderate/severe exacerbations of COPD ADV: 1.1 Sal: 1.59 (Treatment ratio 0.696; *P* <0.001) **Secondary Endpoints:** Time to first moderate/severe exacerbatio 27% Risk reduction with ADV [(HR 0.726 (*P* <0.001)] COPD exacerbations requiring OCS ADV 0.81 Sal 1.23(Treatment ratio 0.657*P* <0.001)	• The most common AEs across both groups were nasopharyngitis and pharyngolaryngeal pain which occurred in a similar percentage of patients in each group. • Pneumonia occurred more frequently in the ADV group (7% ADV and 2% Sal). • Dysphonia (5% ADV and 1% Sal), candidiasis-related events (6% ADV and <1% Sal) occurred more frequently with ADV.

*minimal clinically important change = 1.7 units; †minimal clinically important change = 10 units

MC=multicenter; R=randomized; DB=double-blind; PG=parallel-group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=salmeterol; PBO=placebo; COPD=chronic obstructive pulmonary disease; ATS=American Thoracic Society; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; AM=morning; PEF=peak expiratory flow; TDI=transition dyspnea index; CRDQ=chronic respiratory disease questionnaire; AE=adverse events; OCS=oral corticosteroid

Table 85. Clinical Summary Table of *Advair Diskus* 500/50 versus the Individual Components (Fluticasone Propionate or Salmeterol alone) in Patients with COPD

Ref	Design & Dura-tion	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Calver-ley[48,172]	MC, R, DB, PG, PC 3 years	6184 (mean age=65 years)	ADV (*Diskus*) 500/50 BID FP (*Diskus*) 500 mcg BID Sal (*Diskus*) 50 mcg BID PBO (*Diskus*) BID	• COPD diagnosis • 40-80 years of age • Current or former smoker with a smoking history of ≥10 pack-years • FEV_1 ≤60% predicted, with ≤10% reversibility in predicted FEV_1 • $FEV_1/FVC \leq 70\%$	**Primary Endpoint:** All-cause Mortality Over 3 Years (ADV vs. PBO): HR: 0.825 (95% CI 0.681-1.002); *P*=0.052 **Secondary Endpoints:** Rate of Moderate/Severe COPD Exacerbations (mean rate per patient per year): ADV: 0.85 FP: 0.93 Sal: 0.97 PBO: 1.13 *P*≤0.024 ADV vs. FP, Sal, & PBO	• 3-year probability of having pneumonia was 19.6% for ADV and 18.3% for FP vs. 12.3% for PBO (*P*<0.001 for each comparison); 13.3% for Sal (NS vs. PBO); deaths from pneumonia occurred in 8 patients in the ADV group, 13 FP, 9 Sal, 7 PBO. • No increased cardiac AEs reported on any treatment compared with PBO • No significant difference in probability of bone fracture (ADV 6.3%, FP 5.4%, Sal 5.1%, PBO 5.1%) • In a safety subset, mean percent change in BMD at 3 years (total hip) was -3.2% for ADV, -2.9% for FP, -1.7% for Sal, and -3.1% for placebo (all *P*>0.05) • In a safety subset, no significant differences in development of cataracts glaucoma, or related disorders on any treatment compared with PBO

*negative scores indicate improvement; minimal clinically important difference = 4 units

MC=multicenter; R=randomized; DB=double-blind; PG=parallel-group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=Salmeterol; PBO=placebo; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; HR==Hazard Ratio; CI=Confidence Interval; SGRQ=St. George's Respiratory Questionnaire; HPA=Hypothalamic-Pituitary-Adrenal; AE=adverse event; BMD=bone mineral density; PEF=peak expiratory flow; TDI=transition dyspnea index; CBSQ=Chronic Bronchitis Symptoms Questionnaire

Ref	Design & Dura-tion	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Calverley (cont.)					Quality of Life - Measured by SGRQ (adjusted mean change from baseline): ADV: -3.0 FP: -1.8 Sal: -0.8 PBO: +0.2 $P \leq 0.017$ ADV vs. FP, Sal & PBO	
*negative scores indicate improvement; minimal clinically important difference = 4 units MC=multicenter; R=randomized; DB=double-blind; PG=parallel-group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=Salmeterol; PBO=placebo; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; HR==Hazard Ratio; CI=Confidence Interval; SGRQ=St. George's Respiratory Questionnaire; HPA=Hypothalamic-Pituitary-Adrenal; AE=adverse event; BMD=bone mineral density; PEF=peak expiratory flow; TDI=transition dyspnea index; CBSQ=Chronic Bronchitis Symptoms Questionnaire						

Ref	Design & Dura-tion	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Calver-ley[157,220]	MC, R, DB, PG, PC 12 months	1465 (mean age=63 years)	ADV (*Diskus*) 500/50 BID FP (*Diskus*) 500 mcg BID Sal (*Diskus*) 50 mcg BID PBO (*Diskus*) BID	• Current or former smoker (≥10 pack years) • COPD diagnosis • $FEV_1/FVC \leq 70\%$ (and baseline FEV_1 25-70% predicted and increased <10% after albuterol) • Symptoms of chronic bronchitis • History of COPD exacerbation (at least 1/year in previous 3 years and ≥1 in the last year)	**Primary Endpoint:** Mean Pretreatment FEV_1 (change from baseline): ADV: 113 ml (10%) FP: 7 ml (2%) Sal: 15 ml (2%) PBO: -60 ml (-3%) *P*<0.001 ADV vs FP, Sal, & PBO **Secondary Endpoints:** Rate of Moderate/Severe COPD Exacerbations (mean rate per patient per year): ADV: 0.97 FP: 1.05 Sal: 1.04 PBO: 1.30 *P*< 0.0001 ADV vs. PBO	• All treatments were well tolerated with no difference in the frequency of adverse events except for increased reports or oropharyngeal candidiasis in ADV and FP groups (8% and & 7%, respectively, vs. 2% each for Sal and PBO) • Bruising and clinically significant falls in serum cortisol concentration were similar between groups

*negative scores indicate improvement; minimal clinically important difference = 4 units

MC=multicenter; R=randomized; DB=double-blind; PG=parallel-group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=Salmeterol; PBO=placebo; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; HR==Hazard Ratio; CI=Confidence Interval; SGRQ=St. George's Respiratory Questionnaire; HPA=Hypothalamic-Pituitary-Adrenal; AE=adverse event; BMD=bone mineral density; PEF=peak expiratory flow; TDI=transition dyspnea index; CBSQ=Chronic Bronchitis Symptoms Questionnaire

Ref	Design & Dura-tion	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Calverley (cont.)					Quality of Life - Measured by SGRQ (Adjusted Mean Treatment Difference)*: ADV vs. PBO: -2.2 ADV vs. FP: -1.4 ADV vs. Sal:-1.1 $P \leq 0.021$ ADV vs. PBO & FP	
*negative scores indicate improvement; minimal clinically important difference = 4 units MC=multicenter; R=randomized; DB=double-blind; PG=parallel-group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=Salmeterol; PBO=placebo; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; HR==Hazard Ratio; CI=Confidence Interval; SGRQ=St. George's Respiratory Questionnaire; HPA=Hypothalamic-Pituitary-Adrenal; AE=adverse event; BMD=bone mineral density; PEF=peak expiratory flow; TDI=transition dyspnea index; CBSQ=Chronic Bronchitis Symptoms Questionnaire						

Ref	Design & Dura-tion	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Kardos[208]	MC, R, DB, PG 44 weeks	994 (mean age=64 years)	ADV (*Diskus*) 500/50 BID Sal (*Diskus*) 50 mcg BID	• ≥40 years of age • Post-bronchodilator FEV_1 <50% of predicted • $FEV_1/FVC \leq 70\%$ of predicted • Smoking history ≥10 pack-years • Documented history of ≥2 moderate to severe COPD exacerbations during the last year before the study	**Primary Endpoint:** Rate of Moderate/Severe COPD Exacerbations (mean rate per patient per year): ADV: 0.92 Sal: 1.4 $P < 0.0001$ **Secondary Endpoints:** Post-bronchodilator FEV_1 (change from baseline): ADV: 0.07 L Sal: 0.05 P = NS Morning pre-brochodilator PEF (change from baseline): ADV: 18.0 L/min Sal: 4.4 L/min $P < 0.0001$ Quality of Life (as measured by SGRQ)* ADV: -2.9 L Sal: -0.7 $P = 0.0126$	• Drug-related AEs were reported in 9.7% of patients with ADV and 8.2% with Sal • Oropharyngeal candidiasis was the most frequent drug-related AE with ADV • 23 cases of suspected pneumonia were observed in the ADV group and 7 in the Sal group

*negative scores indicate improvement; minimal clinically important difference = 4 units

MC=multicenter; R=randomized; DB=double-blind; PG=parallel-group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=Salmeterol; PBO=placebo; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; HR==Hazard Ratio; CI=Confidence Interval; SGRQ=St. George's Respiratory Questionnaire; HPA=Hypothalamic-Pituitary-Adrenal; AE=adverse event; BMD=bone mineral density; PEF=peak expiratory flow; TDI=transition dyspnea index; CBSQ=Chronic Bronchitis Symptoms Questionnaire

Ref	Design & Dura-tion	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Mahler[159,221]	MC, R, DB, PG, PC 24 weeks	691 (mean age=62-64 years)	ADV (*Diskus*) 500/50 BID FP (*Diskus*) 500 BID Sal (*Diskus*) 50 BID PBO (*Diskus*) BID	• ≥40 years of age • Current or former smoker (≥20 pack years) • COPD diagnosis • FEV_1/FVC ≤70% (and baseline FEV_1 <65% predicted but >0.7 L) • Symptoms of chronic bronchitis • Moderate dyspnea	**Primary Endpoints:** Mean Morning Pre-dose FEV_1 (change from baseline at endpoint): ADV: 156 ml (15%) FP: 109 ml (11%) Sal: 107 ml (10%) PBO: -4 ml (2%) *P*<0.05 ADV vs FP, Sal & PBO Mean 2-Hour Postdose FEV_1, (change from baseline at Endpoint): ADV: 261 ml (24%) FP:138 ml (13%) Sal: 233 ml (22%) PBO 28 ml (4%) *P*<0.001 ADV vs FP & PBO **Secondary Endpoints:** • Significantly greater improvements in PEF and dyspnea (as measured by TDI) with ADV vs. Sal, FP, & PBO	• Incidence of AEs was similar between groups except for an increase in oral candidiasis in the ADV & FP groups • Incidence of HPA axis or clinically significant ECG abnormalities was similar between treatment groups

*negative scores indicate improvement; minimal clinically important difference = 4 units

MC=multicenter; R=randomized; DB=double-blind; PG=parallel-group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=Salmeterol; PBO=placebo; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; HR==Hazard Ratio; CI=Confidence Interval; SGRQ=St. George's Respiratory Questionnaire; HPA=Hypothalamic-Pituitary-Adrenal; AE=adverse event; BMD=bone mineral density; PEF=peak expiratory flow; TDI=transition dyspnea index; CBSQ=Chronic Bronchitis Symptoms Questionnaire

Ref	Design & Dura-tion	# Pts (Age)	Dose/ Schedule	Inclusion Criteria	Efficacy Results	Safety Results
Mahler (cont.)					• Significantly reduced supplemental albuterol use with ADV vs. FP & placebo • Significantly more nights with no awakenings and fewer symptoms of chronic bronchitis as measured by CBSQ with ADV vs. PBO • No significant differences between treatment groups in exacerbation endpoints • Patients treated with ADV experienced clinically meaningful increases from baseline in overall COPD-related quality of life as measured by the CRDQ that were statistically significantly greater compared with PBO & FP	

*negative scores indicate improvement; minimal clinically important difference = 4 units

MC=multicenter; R=randomized; DB=double-blind; PG=parallel-group; PC=placebo-controlled; ADV=*Advair*; BID=twice daily; FP=fluticasone propionate; Sal=Salmeterol; PBO=placebo; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; HR==Hazard Ratio; CI=Confidence Interval; SGRQ=St. George's Respiratory Questionnaire; HPA=Hypothalamic-Pituitary-Adrenal; AE=adverse event; BMD=bone mineral density; PEF=peak expiratory flow; TDI=transition dyspnea index; CBSQ=Chronic Bronchitis Symptoms Questionnaire